Self-assembling Nanomedicine for Oncology

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First generation – solution (classical injectable)
(for water-insoluble drug, forcible solubilization into water using solubilizer, eg. surfactants, cyclodextrins)

Second generation – Drug physically encapsulated into nanoparticle carrier

Third generation – Drug chemically linked to nanoparticle carrier (Prodrug)
Factors influencing drug availability

How to modulate unbound drug concentration:

a) Minimizing the nanomedicine capture by RES (PEGylation),
b) sustained drug release from carrier (Prodrug approach)

Longer the blood residence time of drug, slower is the clearance, sustained/optimum unbound drug conc, and better is the therapeutic activity and safety.
Carrier-mediated prodrugs

- **Polymeric** eg. polysaccharides, polyhydroxyesters, poly(aminoacid)s etc.
- **Lipidic** eg. Fatty acids, non-fatty acids, terpenoids etc.
- **Others** eg. antibodies, peptides for specific application (cell penetration or targeting) etc.
Carrier-mediated prodrugs

Advantages:
- Sustained drug release, hence improved pharmacokinetic profile
- Protect drugs from rapid metabolic inactivation
- Reduced non-specific biodistribution, selective activation inside the tumor
- Improved transport to the tumor site
- Improved efficacy and safety

Limitations:
- Solubility-related issues, necessitating their encapsulation into delivery carriers
- New Chemical Entity – needs full development program
Carrier-mediated prodrug technology in pharmaceutical development

- **Molecule off-patent**
- **Molecule patent**
- **Prodrug technology**
- **Discovery** → **Development** → **Clinical trials**
- **Approved for marketing**

LCM – Life Cycle Management
Factors influencing engineering of prodrug nanomedicine

- Chemical purity
- Physical nature (crystalline/amorphous)
- Solubility in organic solvents
- Stability in organic solvents
- Stability at process conditions (light/temperature/sonication etc.)
Manufacture of prodrug nanomedicine

1. Top down technique – size reduction of drug crystals

Limitations:
- Non-crystalline prodrugs cannot be milled (e.g., some lipidic/polymeric prodrugs)
- Issues with temp-sensitive prodrugs
2. Bottom-up technique(s) – controlled precipitation in aqueous medium
   a) Nanoprecipitation

- Drug + water-miscible volatile organic solvent
- Aqueous phase
- Controlled precipitation
- Nanodispersion
- Organic solvent elimination
- Pure nanodispersion
- Terminal sterilization or Asceptic processing, and Freeze drying
Limitations
Prodrugs insoluble in organic solvents could not be processed
Safety issues associated with the use of organic solvents
The leaky endothelial vasculature in tumor affected areas facilitate the infiltration of prodrug nanoparticles into tumors. This phenomenon is called EPR effect.
Squalenoyl prodrug nanomedicines - a lipidic prodrug approach

Squalene - a biological lipid (precursor of CHOL biosynthesis)
Squalenoyl prodrug nanomedicines

- Squalenoyl prodrugs assemble into nanoparticles in water
- Enhanced drug loading could be achieved with squalenoyl prodrug approach (squalene being a small molecule)

Example: Squalenoyl gemcitabine


CryoTEM (130nm) Molecular modeling

Pharmacokinetics & anticancer activity of Squalenoyl gemcitabine

Plasma conc after single dose i.v. inj in mice

Antitumor efficacy after 4-dose i.v. inj in tumor mice

Tumor histology

Untreated

Gem-treated

SQgem NA-treated

Tumor immuno-histochemistry

Future of prodrug nanomedicines

PEG (to provide hydrophilic surface)

Targeting nanoparticle

Cell targeting moiety

Imaging agent

Theragnostic nanoparticle

Toward personalized medicine
Conclusion & prospective

- Self-assembling prodrugs could be an effective tool to deliver potent but water-insoluble new molecules at discovery stage or for LCM of commercialized drugs to offer improved biopharmaceutical profile.

- This approach offers opportunity for developing efficient and safer medicines.

- The clinical reach of various oncology prodrugs like Opaxio, Taxoprexin, Elacytarabine, AP5346 (HPMA copolymer–DACH platinate analogue) etc. has renewed considerable interest in this area and hence more prodrugs could be expected in pipeline.

- Development of multifunctional self-assembling prodrug nanomedicines that possess both drug targeting and imaging/diagnostic functionalities are expected to provide opportunities for personalized therapy.
Back-up slides
Carrier-mediated anticancer prodrugs approved or in clinical development

<table>
<thead>
<tr>
<th>Prodrug/conjugates</th>
<th>Company/name</th>
<th>Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymeric</strong></td>
<td></td>
<td></td>
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<tr>
<td>PEG-asparaginase</td>
<td>Enzon (Oncospar)</td>
<td>AML</td>
<td>Approved in 1990</td>
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<tr>
<td>Styrene Maleic Anhydride-Neocarzinostatin (SMANCS)</td>
<td>Yamanouchi (Zinostatin Stimaler)</td>
<td>Hepatocellular carcinoma</td>
<td>Approved in 1990 in Japan</td>
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<tr>
<td>Poly(glutamic acid-paclitaxel)</td>
<td>Cell Ther (Opaxio)</td>
<td>NSCLC</td>
<td>Filed EMEA</td>
</tr>
<tr>
<td>PEGylated-anti VEGFR2 Fab fragments as angiogenesis inhibitor</td>
<td>UCB Pharma (CDP 791)</td>
<td>NSCLC</td>
<td>Phase II</td>
</tr>
<tr>
<td>HPMA-DACH platinate analogue</td>
<td>Access Pharma (AP5346)</td>
<td>Solid tumours</td>
<td>Phase II</td>
</tr>
<tr>
<td>PEG-poly(Aspartic Acid)-Doxorubicin Micelles</td>
<td>NK911</td>
<td>Solid tumours</td>
<td>Phase II</td>
</tr>
<tr>
<td>HPMA copolymer–GFLG–doxorubicin</td>
<td>FCE 28068</td>
<td>Solid tumours</td>
<td>Phase I/II</td>
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<tr>
<td>HPMA copolymer–GFLG–doxorubicin–galactosamine</td>
<td>FCE 28069</td>
<td>Solid tumours</td>
<td>Phase I/II</td>
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<tr>
<td>HPMA copolymer–carboplatinate analogue</td>
<td>AP5280</td>
<td>Solid tumours</td>
<td>Phase I/II</td>
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<tr>
<td>Polymer–cyclodextrin nanoparticle–camptothecin</td>
<td>Calando Pharma (IT-101)</td>
<td>Solid tumours</td>
<td>Phase I/II</td>
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<tr>
<td>Polymer–cyclodextrin nanoparticle-siRNA</td>
<td>Calando Pharmaceutical (CALAA-01)</td>
<td>Solid tumours</td>
<td>Phase I</td>
</tr>
<tr>
<td>Polyglutamic acid-Gly-Camptothecin</td>
<td>Cell Ther (CT-2106)</td>
<td>Solid tumours</td>
<td>Phase I (Phase II delayed)</td>
</tr>
<tr>
<td>PEG–docetaxel (intravenous)</td>
<td>Nektar (NKTR-105)</td>
<td>Solid tumours incl. hormone-refractory prostate cancer</td>
<td>Phase I</td>
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</tbody>
</table>

### Lipidic

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<th>Indication</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Elaidic acid-cytarabine</td>
<td>Clavis pharma (Elacytarabine)</td>
<td>AML</td>
<td>Phase II-III</td>
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<tr>
<td>Elaidic acid-gemcitabine</td>
<td>Clavis Pharma (CP-4126)</td>
<td>Pancreatic cancer</td>
<td>Phase II</td>
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<tr>
<td>DHA-paclitaxel</td>
<td>Protarga (Taxoprexin)</td>
<td>Solid tumors</td>
<td>Phase II</td>
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