Getting the best out of Cyclodextrins

CYCLOLAB Ltd.

Solubilization of Panobinostat with cyclodextrins for anticancer therapies
Multiple myeloma

- Cancer of plasma B cells
- These are white blood cells originating from the bone marrow
- The cancerous plasma cells produce abnormal antibodies instead of normal ones
- Causes bone pain, anemia, kidney problems, infection or neurological symptoms

Diffuse Intrinsic Pontine Glioma (DIPG)

- Tumor located in the middle of brain stem
- Glioma is a group term for a tumor that arise from glia
- DIPG is brainstem glioma
- 5-year survival rate: <1%
- Treatments: neurosurgery not possible, radiotherapy, chemotherapy
- Difficulty in treatment, overcoming the blood-brain-barrier (BBB)
Lysosomal storage diseases

- A group of about 50 rare genetically inherited metabolic disorders
- Disrupts the metabolism of lipids, glycoproteins or polysaccharides
- Usually connected to the misbehavior of one specific enzyme
- Few examples: Niemann Pick disease type C, Fabry disease, Hunter syndrome, Gaucher disease

How panobinostat works

- Antineoplastic agent, Histone deacetylase (HDAC) inhibitor
- DACs are overexpressed in myeloma patients
- Inducing apoptosis of malignant cells: cell death
- Similar action in the case of lysosomal storage diseases

Panobinostat

- **Trade name:** Farydak (Novartis)
- Antineoplastic agent, Histone deacetylase inhibitor, inducing apoptosis of malignant cells
- **Indication:** for cancer treatment (multiple myeloma)
- Fast absorption from the gut, but low bioavailability (21%) due to first-pass effect
- 315 major drug interactions, 209 moderate drug interactions

- Clinical stage indications:
  - Lymphomas
  - Graft versus Host Disease
  - HIV/AIDS
  - Glioma
  - Lysosomal Storage Disease (Niemann Pick Type C)
Market forecast

Panobinostat forecasted sales from Farydak

Source: Globaldata, data based on predicted Farydak sales
Structure of Panobinostat

- Hydroxamic acid compound
- Water Solubility: 0.002 mg/mL (estimated)
- logP: 2-3

- Patients receive **oral** Panobinostat in **capsules** with 10-15-20 mg API
- No injections were developed due to the low aqueous solubility
Panobinostat with cyclodextrins (IP background)

  WO2017167837A1 Patent in investigational phase
  EP3347055 Decision was made to grant a European patent (2019)

Uses Hydroxypropyl beta-cyclodextrin (HPBCD)

Brain tumor

Midatech (Cardiff): An R&D company focused on delivering innovative oncology and rare disease products to patients

2019 FDA orphan designation for solubilized form of panobinostat (MTX110) in childhood brain cancer: Diffuse Intrinsic Pontine Glioma (DIPG)

Phase I and Phase II

Midatech Pharma announces confirmation of a €2.6 million EU Grant for further clinical development of MTX110 for the treatment of Diffuse Intrinsic Pontine Glioma, a rare and fatal form of childhood brain cancer
Panobinostat with cyclodextrins (IP background)

- **RaNeDis Pharmaceuticals, LLC (2016)** Claypool; **US201662360012**
  Compositions and methods of treating and/or preventing lysosomal storage diseases and other monogenetic metabolic diseases.
  **WO2018009531** Patent in investigational phase
  Withdrawn in EPO countries
  Using HPBCD and SBECD
  Mainly for vorinostat, Panobinostat is mentioned
  Indication: Niemann Pick C and other lysosomal storage diseases

- **RaNeDis Pharmaceuticals, LLC (2017)** Claypool; **US201762516251**
  Compositions and methods of treating and/or preventing cancer
  **WO2018226939A1** Patent in investigational phase
  Using HPBCD and SBECD
  Mainly for vorinostat, Panobinostat is mentioned
  Indication: brain tumor

- **Rare and Neglected Diseases**
  - RND-001 formulation has resulted in dramatic improvements of function and survival in a mouse transgenic model of Niemann-Pick Type C disease. Licensed from the Univ. Of Notre Dame.

ref: [https://www.ranedis.com/](https://www.ranedis.com/)
Clinical studies of Panobinostat

- **Midatech Pharma**: MTX110 panobinostat in solution
  - Brain Cancer (Phase I/II)

- **Novartis**: Farydak tablets
  - *Multiple Myeloma (Approved)*
  - AIDS (Phase I/II)
  - Brain Cancer (Phase I/II)
  - Breast Cancer (Discovery)
  - Graft Versus Host Disease (Phase I/II)
  - Huntington’s Disease (Pre-clinical)
  - Kidney Cancer (Phase I/II)
  - Lung Cancer (Phase I)
  - Pancreatic Cancer (Discovery)
  - Prostate Cancer (Phase II)
  - Sickle Cell Anemia (Phase I)
  - Soft Tissue Sarcoma (Phase I)
  - Solid Tumors (Phase I)
  - Thyroid Cancer (Phase II)

Ref: Biopharm Insight
Formulation of Panobinostat with cyclodextrin

- **Midatech**
  - 40 µM Panobinostat with HPBCD, which is **0.11 mg/ml**
  - **Panobinostat** in solution
  - Formulation is a lyophilized powder
  - In one **clinical trial** a dose of 0.5 ml of 300 µM (**0.85 mg/ml**) MTX-001 solution is used
  - In another **clinical trial** 30-60-90 µM MTX-001 is used (Panobinostat), the highest concentration is **0.26 mg/ml**

- **Ranedis**
  - examples only with vorinostat
  - RND001 is not Panobinostat
  - They use HPBCD and SBECDD for solubilization (up to 5 mg/ml)
Cyclolab’s procedure

10 mg/ml Panobinostat is achievable in solution

The technology improvements invented at Cyclolab enable successful circumvention of all existing patents in this field.
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