

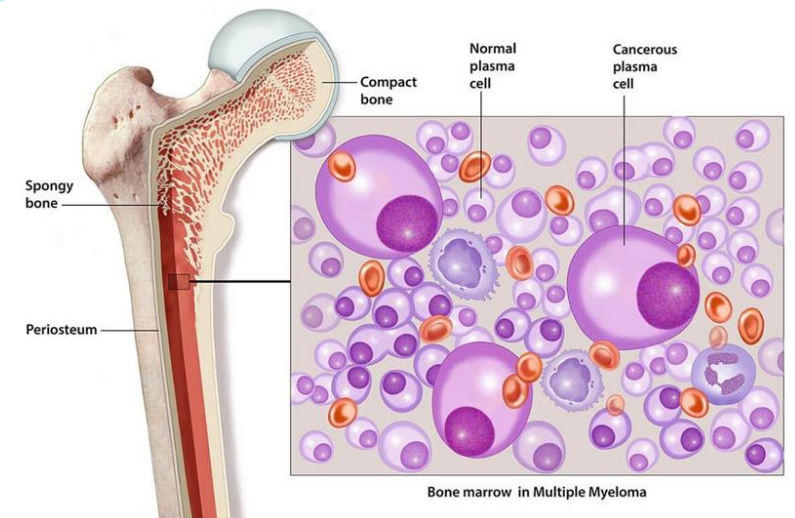
GETTING THE BEST OUT OF CYCLODEXTRINS

Formulation of **Panobinostat**



Multiple myeloma

- Cancer of plasma B cells
- They 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



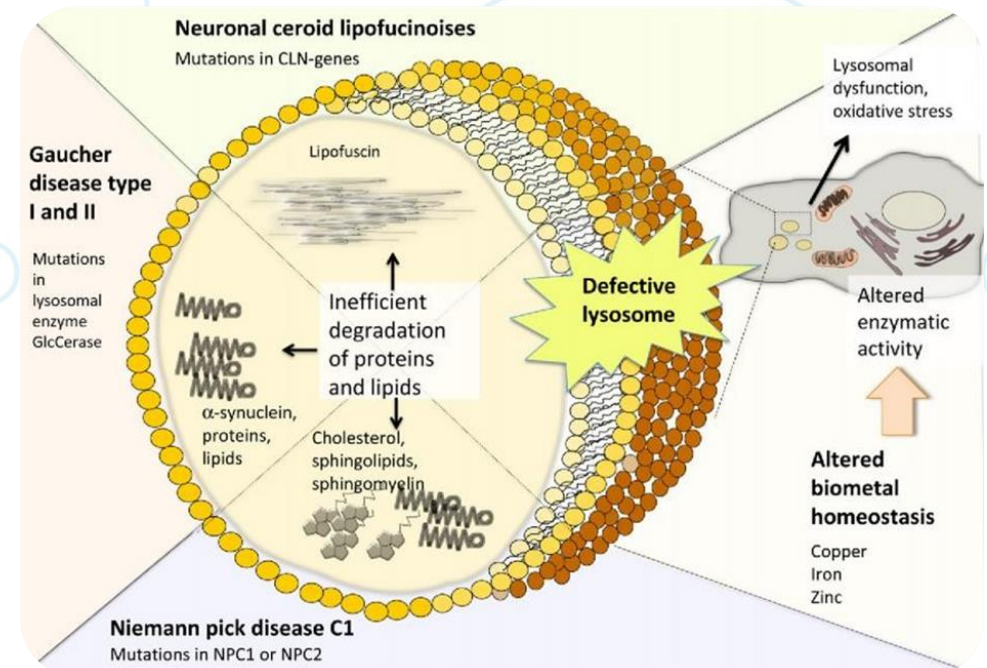
Diffuse Intrinsic Pontine Glioma (DIPG)

- 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-brainbarrier (BBB)



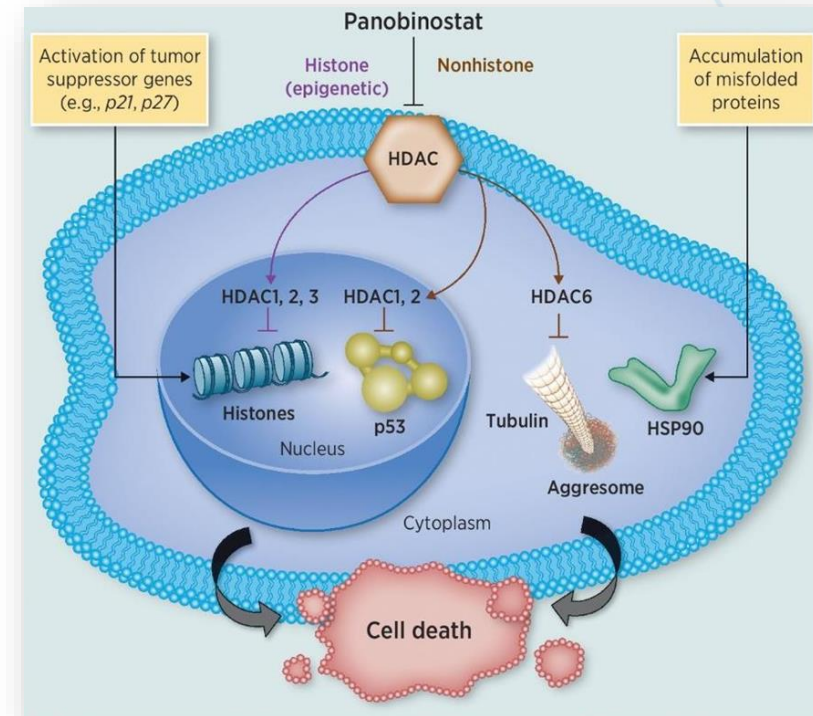
Lysosomal storage diseases

- 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

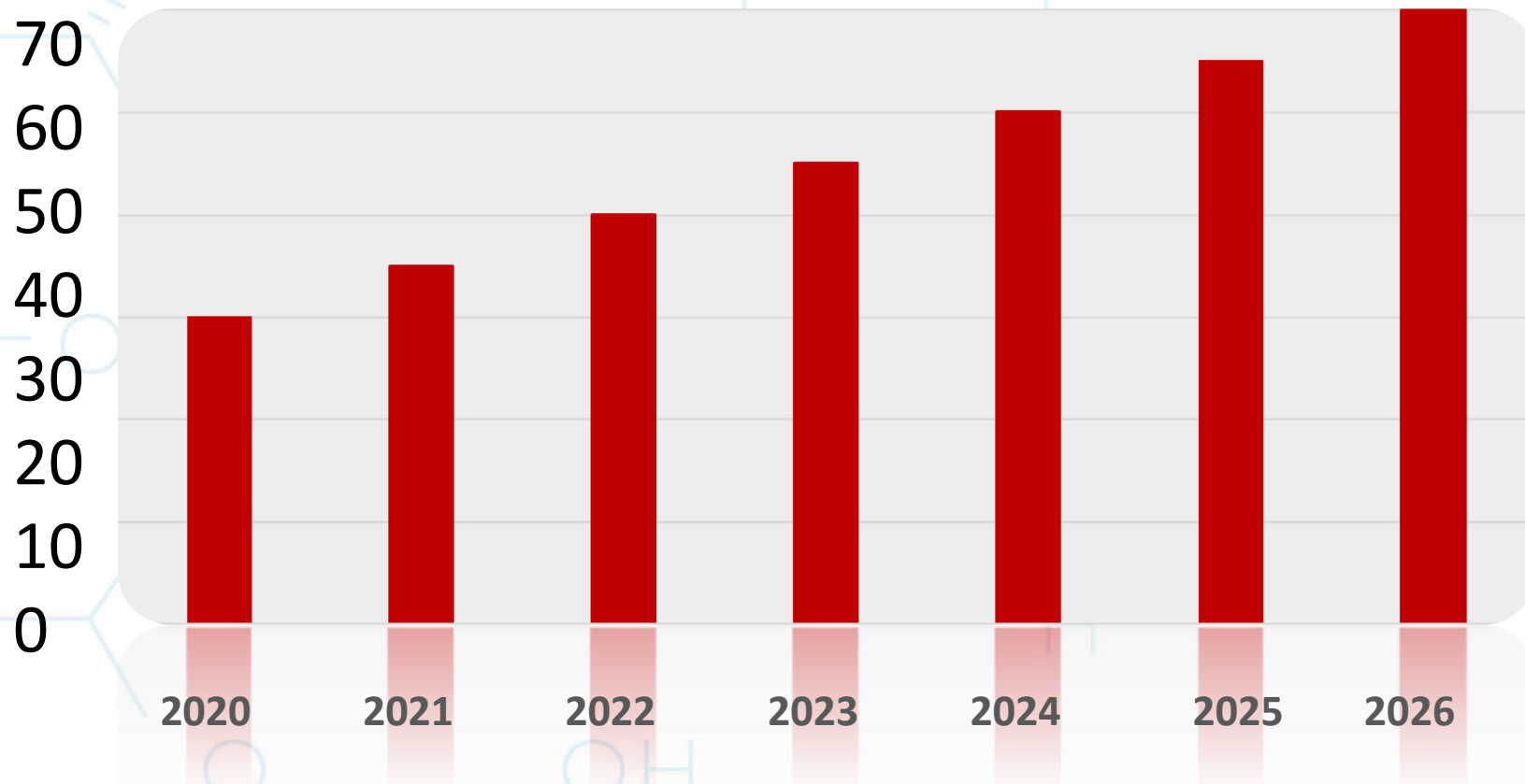
Clinical stage indications:

- Lymphomas
- Graft versus Host Disease
- HIV/AIDS
- Glioma
- Lysosomal Storage Diseases
(Niemann Pick Type C)



Market forecast

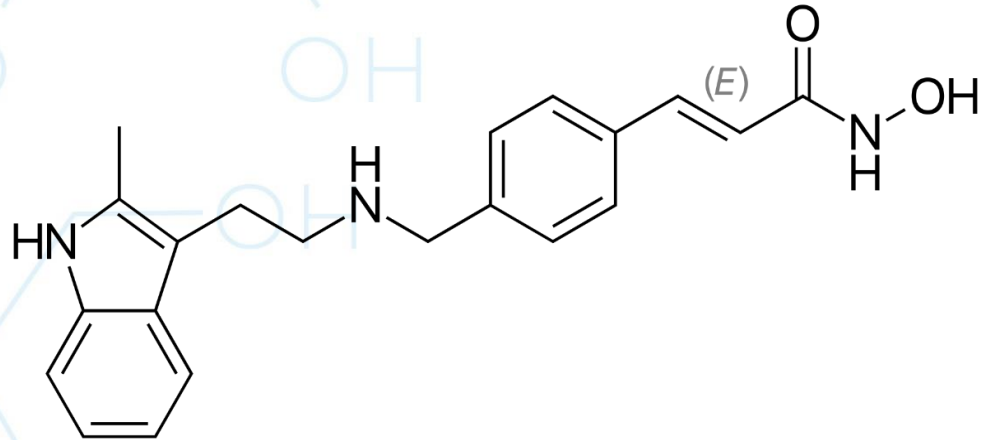
Panobinostat forecasted sales from Farydak



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)

Midatech Pharma Ltd., (2016) Coulter et al.; GB20160005406
Cyclodextrin-panobinostat adduct
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

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.

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

ref: <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)
- Huntingtons 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)

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 SBECED for solubilization (up to 5 mg/ml)

CycloLab

- **10 mg/ml Panobinostat**
- is achievable in solution
- The technology improvements invented at CycloLab enable successful circumvention of all existing patents in this field.

CD-enabled panobinostat

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