Pharmaceutical Drug Development in Neuroblastoma
- From Bench to Bedside -

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Targeted Anticancer Drug Development Approach

TARGETS

FDA-approved Drugs

- ODC

INHIBITORS

- DFMO
  - Neuroblastoma Phase II Clin Trial

Novel Natural Products

- Proteasome

- Syringolin A
  - Neuroblastoma Patent/Pharma
DFMO may be re-purposed for the treatment of (MYCN-driven) neuroblastoma

ODC is “novel” drug target, not clinically explored in neuroblastoma
History and Use of DFMO

**DFMO (Eflornithine, Ornidyl™)**

**HISTORY:** DFMO developed by scientists at Merrell-Dow in 1978

**Common USE:**
- West African Sleeping Sickness (Trypanosomiasis)
- Facial Hirsutism (Vaniqua) (FDA-approved)
- Neuroblastoma, Colon Cancer (Therapy & Chemoprevention)
Consortium - NMTRC Children’s Hospitals

- Helen DeVos Children’s Hospital
- Children’s Mercy Hospitals & Clinics
- Texas Children’s Cancer and Hematology Centers
- Kapi‘olani Medical Center for Women & Children
- National Cancer Institute
- Phoenix Children’s Hospital
- Levine Children’s Hospital
- Dell Children’s Medical Center of Central Texas
- MUSC Children’s Hospital
- Cardinal Glennon
- Intermountain Primary Children’s Medical Center
- Penn State Hershey Children’s Hospital
- Connecticut Children’s Medical Center
- Children’s Hospitals and Clinics of Minnesota
- Arnold Palmer Hospital for Children
- Monroe Carell Jr. Children’s Hospital at Vanderbilt
Phase I Clinical Trial – NMTRC Multicenter Study

Safety Study for Refractory or Relapsed Neuroblastoma with DFMO Alone and in Combination with Etoposide

Principal Investigator: Giselle Sholler, MD
Co-Investigator: André Bachmann, PhD

Trial opened in February 2010
Phase II Clinical Trial – NMTRC Multicenter Study

A Phase II Preventative Trial of DFMO as a Single Agent in Patients with High-Risk Neuroblastoma in Remission

Principal Investigator: Giselle Sholler, MD
Co-Investigator: André Bachmann, PhD

Trial opened in June 2012
Ongoing Laboratory Research

Identify novel, rationally-selected drug combinations with synergistic anti-proliferative activity
Physical Interaction of ODC and SPR

SPR – ODC

Close-up of intermolecular structure

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  - ODC
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  - Proteasome

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- Syringolin A
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Plant-Derived Anticancer Drugs in Clinical Use

Vinblastine/Vincristine: *Catharanthus roseus* /Jamaica and Philippines (originally from Madagascar)
294/749 clinical trials (1/2014)

Etoposide: *Podophyllum species*/ Eastern US, Himalayas
1,000 clinical trials (1/2014)

Paclitaxel/Docetaxel: *Taxus species*/NW US, Europe
1815/1564 clinical trials (1/2014)

Topotecan/Irinotecan: *Camptotheca acuminata*/China
301/877 clinical trials (1/2014)

Slide provided by Gordon M. Cragg, NCI
Discovery of Syringolin A (SylA)

**Plant Pathogen**  
*Pseudomonas syringae pv. syringae*

Brown Spot Disease  
Bean Plant  
*(Phaseolus vulgaris L)*
Proteasome Inhibition by Novel Binding Mechanism

Co-Crystallization (SylA : 20S core)

2.9 Å

Proteasomal β-Rings

- Caspase-like activity
- Trypsin-like activity
- Chymotrypsin-like activity

SylA

Bortezomib (Velcade®)

Velcade®; FDA approved for the treatment of Multiple Myeloma

In Vivo Effect of Syringolin A in NB Xenografts

Bachmann/Sholler labs, unpublished data
Identify novel, syrbactin-inspired chemical drug analogs to improve potency and bioavailability
Syrbactin-Inspired Analog Design

Prof. Markus Kaiser

Total Synthesis (PNAS, 2009)

Prof. Markus Kaiser
University of Duisburg-Essen

Prof. Michael Pirrung
UC Riverside

Pharma bought our patent and started new Biotech company
Physicians and scientists need to work hand-in-hand, with one common goal, - the patient -
The True Super Heroes

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the hope is, this pill is stopping Lily-Mae’s cancer from coming back