A Phase I study examining the feasibility of intermittent convection-enhanced delivery (CED) of MTX110 for the treatment of children with newly diagnosed diffuse midline gliomas

https://clinicaltrials.gov/ct2/show/NCT04264143

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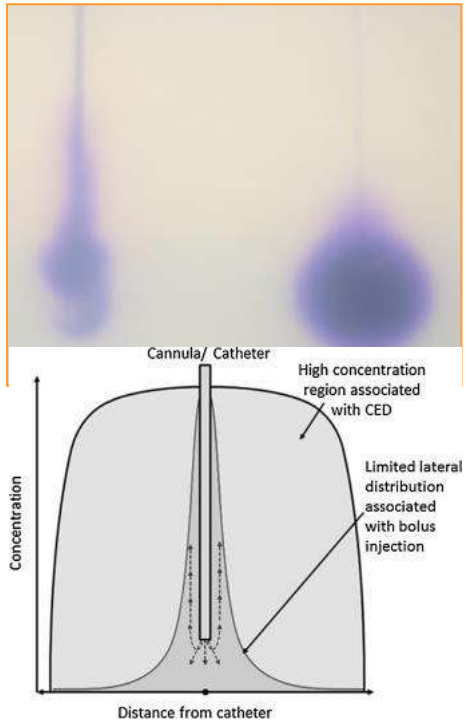
Convection Enhanced Delivery (CED)
Basic Principles

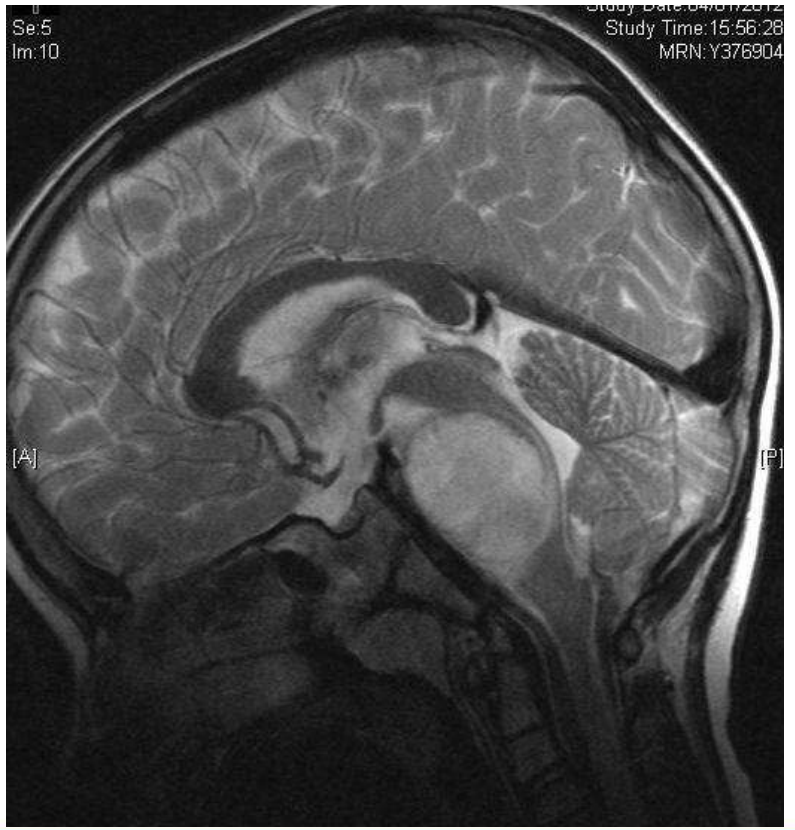
The infusion of drugs under controlled pressure to the brain parenchyma via targeted micro-catheters



- CED utilizes bulk flow rather than diffusion
- Diffuse flow :Fick's law, $J=-D\nabla C$,
- Bulk flow pressure gradient :Darcy's law: $v=-K\nabla p$
- Few cms vs few mms

- infusion rates typically range from 0.1 to 10 µl/min

- Diffuse Intrinsic Pontine Glioma
- 10-20 new patients per year per million population
- Median survival : 9 months
- Radiation therapy is the only standard treatment
- providing benefit in 2/3 patients
- for extra 3-6 months..



El-Khury etal J Neurooncol. 2019 Oct;145(1):177-184.

HDACis and DIPG (Panobinostat,VPA)

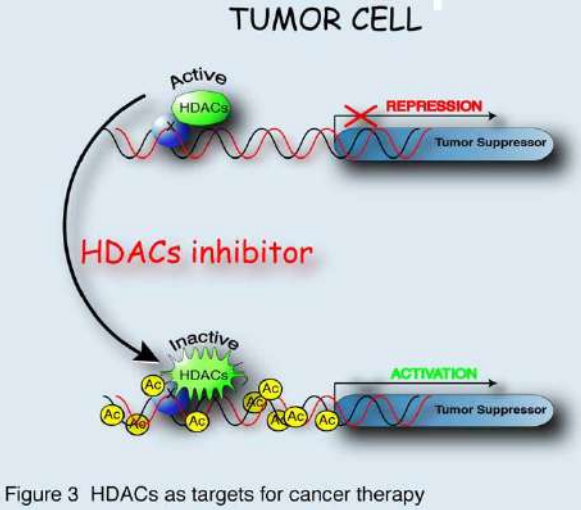
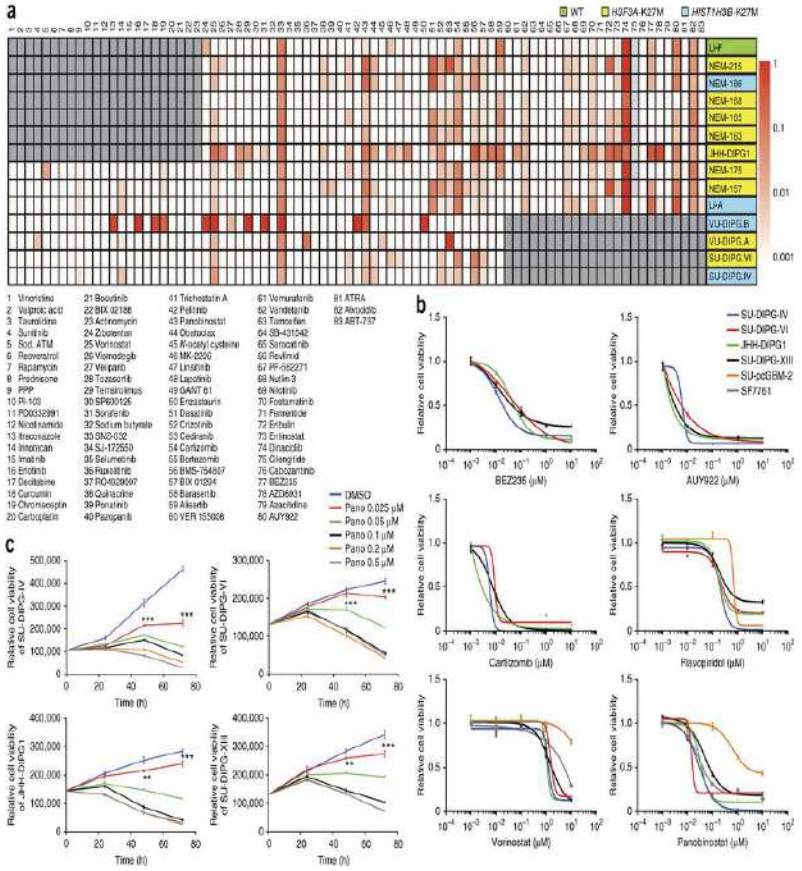


Figure 3 HDACs as targets for cancer therapy



Grasso et al Nat Med. 2015 Jun;21(6):555-9. doi

Convection Enhanced Delivery (CED)
Current Status DIPG
MTX110 preclinical work for CED

- Gills lab investigated the toxicity, distribution, and clearance of a water-soluble formulation of Panobinostat (MTX110) in **Juvenile male Wistar rats (n = 24**)
- Large-animal toxicity was investigated using a clinically relevant MRI-guided translational porcine model of CED in which a drug delivery system designed for humans was used.

- Panobinostat was administered at 30 mM to the ventral pons of 2 juvenile **Large White–Landrace cross pigs**.

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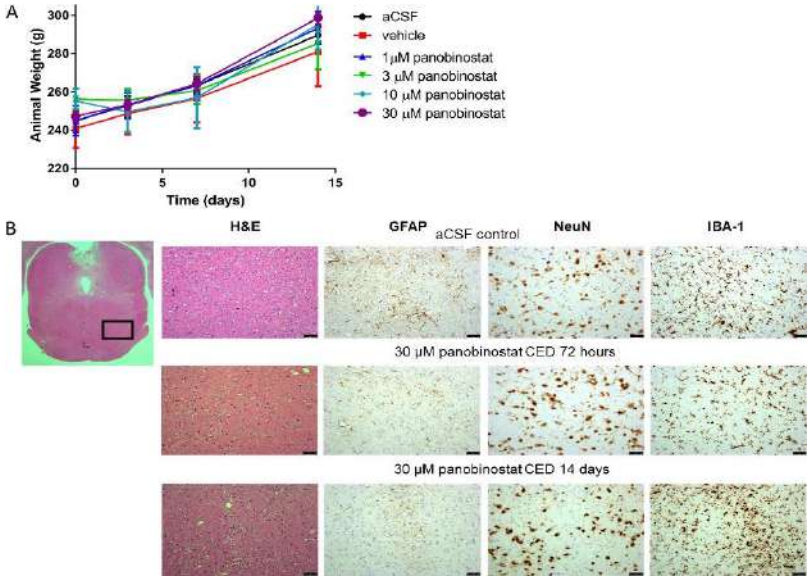
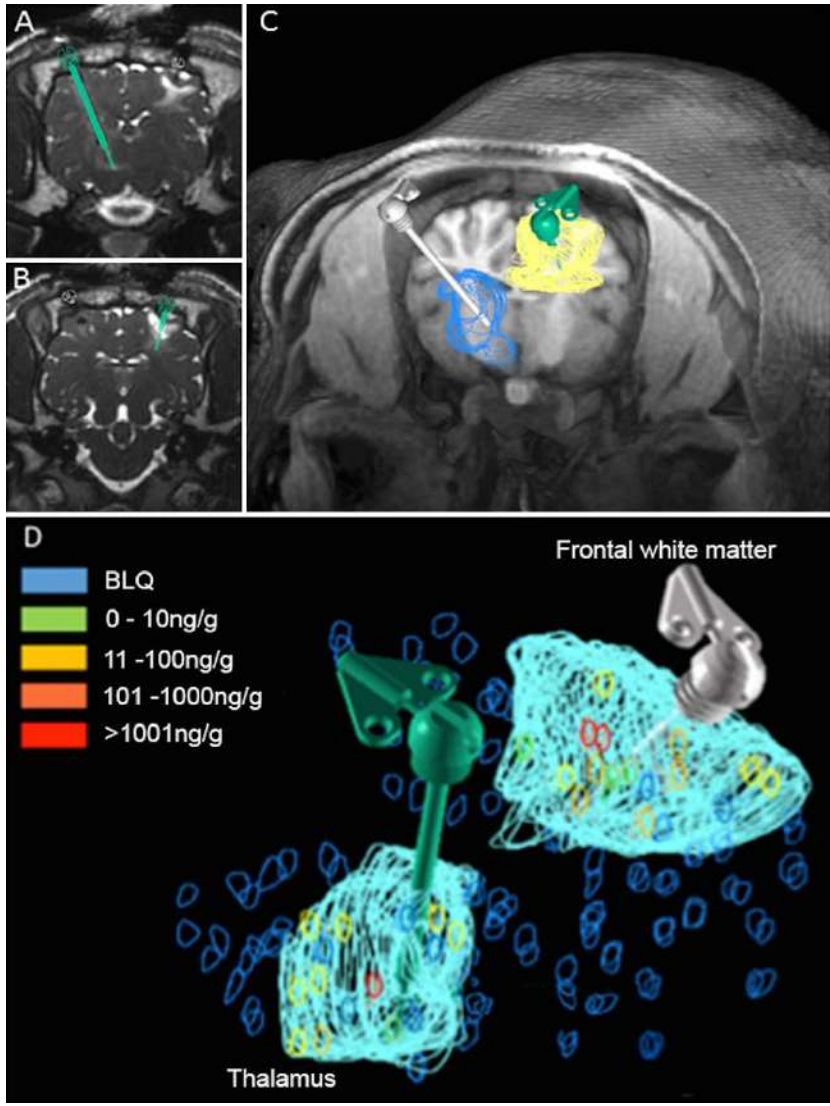
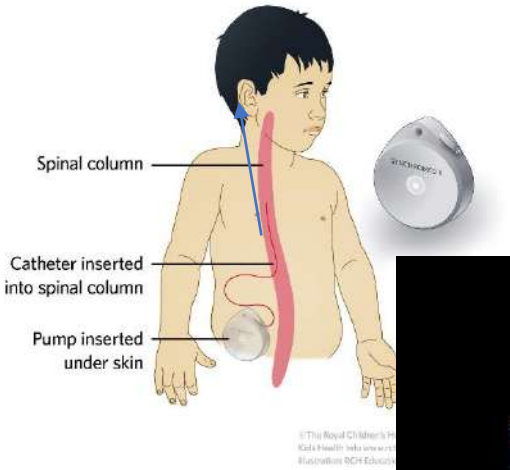




Singleton *et al* J Neurosurg Pediatr. 2018 Sep;22(3):288-296

Open at Columbia University Medical Center

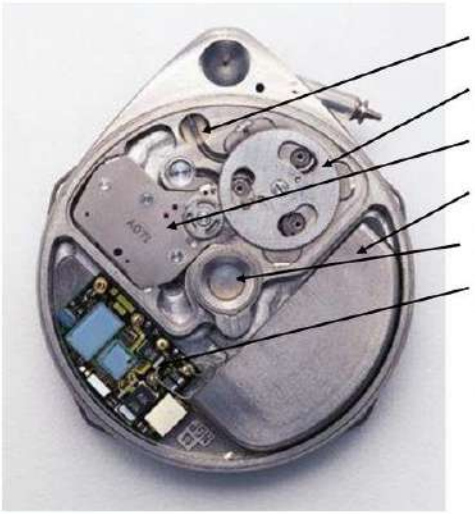


Trial Title

A Phase I study examining the feasibility of intermittent convection-enhanced delivery (CED) of MTX110 via ambulatory pump for the treatment of children with newly diagnosed diffuse midline gliomas (DMGs).

Medtronic

Inside Synchromed II...



Innovating for life.

A Phase I study examining the feasibility of intermittent convection-enhanced delivery (CED) of MTX110 via ambulatory pump for the treatment of children with newly diagnosed diffuse midline gliomas (DMGs

Study Objectives

	Objectives	**Outcome measures**
Primary Endpoint	A phase I study to evaluate the safety and Maximum Tolerated Dose (MTD) of chronic MTX110 CED in children with diffuse midline gliomas	Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Secondary Endpoints	To determine the Objective Response Rate with MTX110 via CED in this population	Documentation of response based on Pediatric RANO criteria
	To determine Progression Free Survival (PFS) and Overall Survival (OS)	Documentation of PFS and OS post treatment with IMP
	To determine the steady state volume of drug distribution	Assessment of volumetric and metabolic changes with contrast enhancement intensity on MRI and MR spectroscopy
	To evaluate the quality of life of the family and the patient that is being treated with CED	QoL assessment tool: PedsQL™ 4.0 Brain Tumor Module

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Eligibility- Inclusion Criteria

Diagnostic criteria

- Age more than 3 years up to the 18th birthday
- Radiological diagnosis of DIPG with tumor confined to the region of the pons or bilateral thalami without cystic changes or hematoma obstructing the planned catheter trajectories
- Radiological diagnosis of bithalamic glioma tumor confined to bilateral thalami without cystic changes or hematoma obstructing the planned catheter trajectories
- Radiological features of DIPG: intrinsic, pontine based infiltrative lesion; hypointense in T1 weighted images (T1WIs) and hyperintense in T2 sequences, with mass effect on the adjacent structures and occupying at least 50% of the pons

Prior and concomitant therapy

- No prior therapy is allowed other than involved field radiotherapy (54Gy) and CSF diversion for hydrocephalus, including endoscopic third ventriculostomy (ETV) or a ventriculo-peritoneal shunt.
- No concomitant medicine or therapies for treatment are permitted while the patient is enrolled in this study.

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Eligibility- Inclusion Criteria

Subject characteristics

- Subjects must be healthy enough to tolerate surgery and general anesthesia 14 days or fewer from registration, based on the opinion of the principal investigator. This includes, but is not limited to:
- *Performance status:*
  - Karnofsky performance status or Lansky play score of ≥70 assessed at diagnosis
- *Hepatic:*
  - Total bilirubin: within normal institutional limits
  - AST(SGOT)/ALT(SGPT): ≤ 2.5 × institutional upper limit of normal
- *Renal:*
  - Creatinine: within normal institutional limits
  - Creatinine clearance: ≥ 60 mL/min/1.73m2 for patients with creatinine levels above institutional normal
- *Hematopoietic:*
  - Absolute neutrophil count: ≥ 1,500/µL
  - Platelet count: ≥ 100,000/µL – no transfusion within 7 days
  - Hemoglobin level: ≥ 10g/dL – no transfusion within 7 days
  - PT and APTT: within normal institutional limits
  - No documented current bleeding disorder

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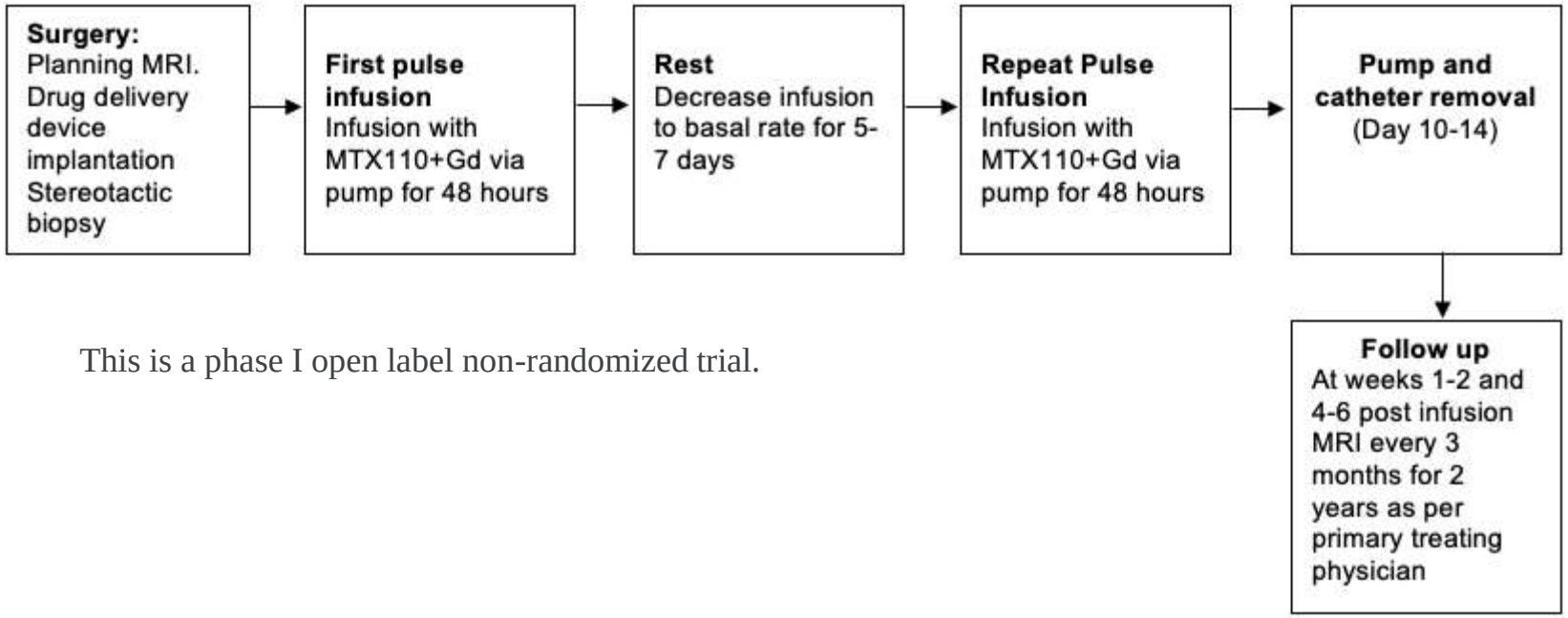
Study Schema



This is a phase I open label non-randomized trial.

- . 2020 Sep;149(2):263-272

Infusion Pulse #1 PINE score monitoring

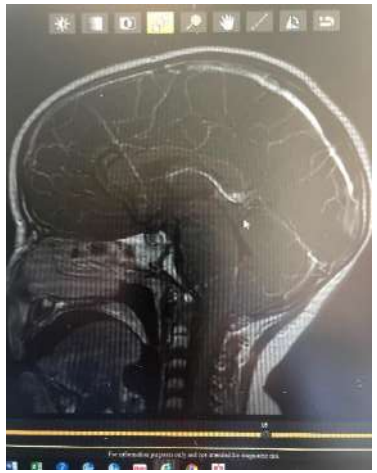
	Symptom	Grade		Symptom	Grade
General	Headache		Cranial Nerves	Visual failure	
	Nausea			Difficulty moving right eye	
	Vomiting			Difficulty moving left eye	
	Mobility			Facial sensory changes	
	Behavioural change			Facial Weakness	
	Mood			Hearing change	
	Incontinence			Communication issues	
	Seizures			Dysphagia	
	Constipation/ Diarrhoea		Long Tracts	Body/limb sensation	
	Fever			R Arm Weakness	
	Breathing problems			L Arm Weakness	
	Hiccoughs			R Leg Weakness	
				L Leg Weakness	

Hollingworth and Zacharoulis
J Neurooncol 2020 Sep;149(2):263-272

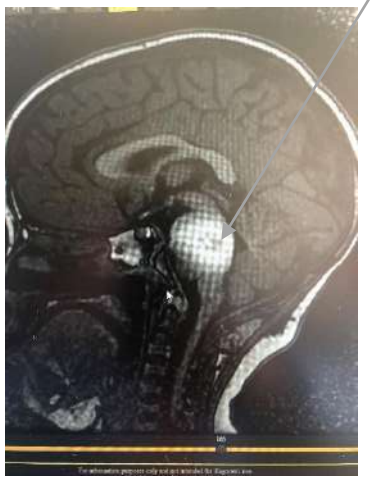
CONVECTION-ENHANCED DELIVERY of MTX110

- 3 patients treated so far at 30 microM
- NO SAEs
- Toxicity: Grade II diplopia (1) Grade I sensation (n=1) , headache Grade II (n=2)

- 1 patient progressed 8 months post treatment



Tumor prior to infusion



After infusion

Acknowledgments

- Neurosurgery — Chankrit Sethi, Rebecca Zylber
- Jeff Bruce
- Neil Feldstein

Gary Yael Foundation

COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK

- Neuropathology
- Peter Cannol
- Neuro-Radiology
- Alexis Maddocks

Hope and Heroes

- Dara Steinberg
- Meghan Tomb