MIDATECH PHARMA

At A Glance

MidaSolve™

Nanotechnology Platform That Makes Medicines Better, Enabling Treatments That Otherwise Would Not Be Possible.

OVERVIEW

The MidaSolve Nano Inclusion (NI) technology is utilized for potent small molecule chemotherapeutics that have minimal solubility at biological pH, which limits them to oral administration in solid form. When reformulated with MIdaSolve technology, the complexed molecules solubilize such that the molecule can be administered in liquid form into the body. This enables local infusion directly into the tumour, thus extending the available routes of administration for drugs that otherwise would be limited to oral forms only.

THE TECHNOLOGY

Many of the small molecule chemotherapeutics that are indicated for solid tumour treatment have minimal solubility ie cannot be dissolved in water or other fluids, at biological pH. This can limit the available routes of administration for a drug which cannot then be administered in liquid format. In some cases, the problem of insolubility can be addressed by formulation in mixtures of water and a solvent such as ethanol or dimethyl sulfoxide (DMSO), but these solvents are toxic to the human body and the solution cannot be used for treatments of example brain cancers (e.g., glioma). Midatech has investigated nano approaches for increasing the aqueous solubility of several classes of cancer therapeutics, and producing complexes that solubilize these agents and enable administration in liquid form directly into tumours.

The complexes comprise a hydrophobic ('water-fearing') inner surface and a hydrophilic ('water-loving') outer surface, and as a result are capable of forming host-guest complexes. A hydrophobic, poorly water-soluble drug can associate with the inner, more hydrophobic surface of the host ring, while the larger hydrophilic outer surface can associate, and solvate, with surrounding water molecules in the liquid form. Such complexes can be particularly stable, depending upon the strength of the host-guest interaction. The key advantage of host-guest complexation is a significant increase in the water solubility of the active compound at biological pH.

Midatech has studied the complexation and solubility-enhancing effects of these nano complexes on certain classes of chemotherapeutics that, because of their insolubility, can not be administered in liquid form. Rather they have to be administered as an oral tablet form, which limits the amount of drug that gets to the tumour site, as well as increasing side effects on the body as it circulates in the system. The first successful host-guest formulation is MTX-110, a water soluble complex 'histone deacetylase inhibitor - panobinostat' for the treatment of brain cancer. The resulting complex is readily soluble in water at therapeutic concentrations thus enabling liquid administration routes directly into the tumour that otherwise would not be possible.

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THE VALIDATION

Diseases

MTX110 is being developed for the treatment of diffuse intrinsic pontine glioma (DIPG) – a fatal childhood brain cancer, and uses the company's MidaSolve technology, which allows for the solubilized local delivery of potent therapeutics directly to the tumor. The active compound is the poorly soluble hydroxamic acid drug panobinostat, a histone deacetylase inhibitor (HDACi), which until recently could not be formulated for parenteral (liquid) administration. Midatech's MidaSolve technology enabled the aqueous solubility of this class of small molecule cancer therapeutic, which expands parenteral delivery options that in turn are expected to improve the safety and efficacy of the treatment. Panobinostat was developed by Novartis and approved in 2015 for the treatment of multiple myeloma; Midatech has licensed panobinostat from Novartis for use in treating Diffuse Intrinsic Pontine Glioma (DIPG) in children, and Glioblastoma Multiforme (GBM) in adults.

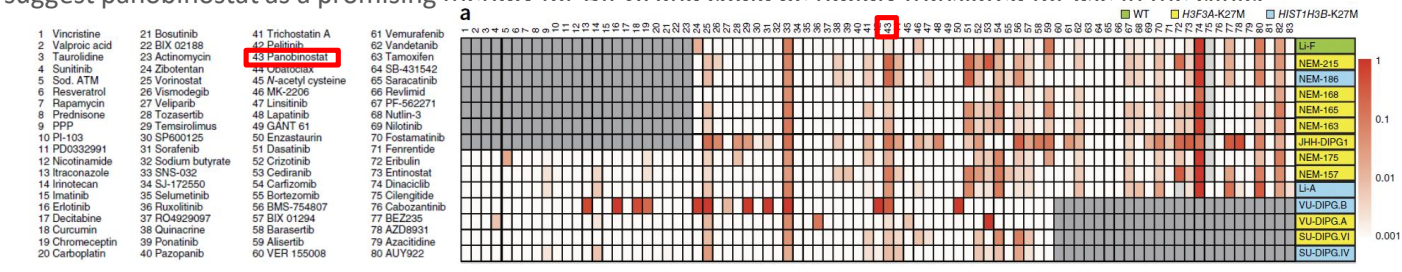
DIPG is a highly infiltrative brainstem high grade glioma that occurs mostly in children. The tumours are aggressively infiltrative such that cancer tissue typically cannot be differentiated from normal brain tissue. The overall median survival of children with DIPG is approximately 9 months, and remains unchanged despite decades of clinical trial research. The only standard of care is palliative focal radiotherapy, but this has minimal effect on survival and essentially all children die of this disease. Surgical resection is unavailable due to the location of the tumour in the brainstem. New therapeutic strategies are urgently needed. Approximately 1,000 individuals worldwide are diagnosed with DIPG each year.

Science

Panobinostat (Farydak®) is a potent, nonselective histone deacetylase inhibitor. It was selected as a potential treatment for DIPG following the screening of 83 drugs against 14 patient-derived DIPG cell cultures (Grasso et al., 2015). The drugs were selected by paediatric neuro-oncologists as either promising targeted agents or traditional chemotherapeutic agents used in paediatric brain tumour therapy. Panobinostat was effective against 12/16 patient derived DIPG cell cultures. But Panobinostat given in its natural oral form does not cross the blood-brain barrier, and thus does not reach brain tumours. MidaSolve allows an alternate means of delivery in liquid form, infused directly into the tumour. Direct delivery of MTX110, the soluble form of panobinostat, bypasses the blood brain barrier and ensures adequate drug exposure to tumour cells. MTX110 molecular targeting and intratumoural delivery thus provides significant potential for treatment of DIPG.

Data

Data from laboratory and animal studies shows significantly improved survival rates. Independent US research conducted identified panobinostat as among the most effective agents screened out of more than 80 chemotherapeutic drugs studied, demonstrating impressive therapeutic efficacy both in vitro and in DIPG orthotopic xenograft models. Combination of genomic data, chemical screening data (heat map graphic below), and animal data suggest panobinostat as a promising therapy for DIPG, and could be rapidly translated for use in the clinic.



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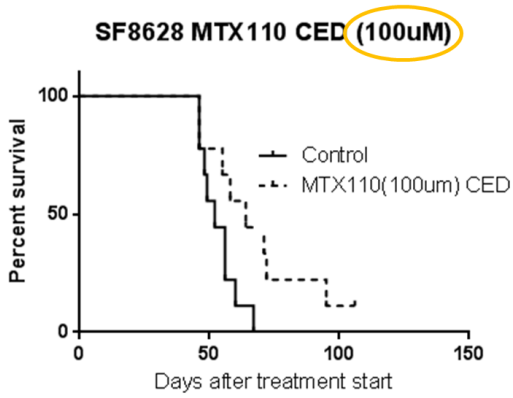
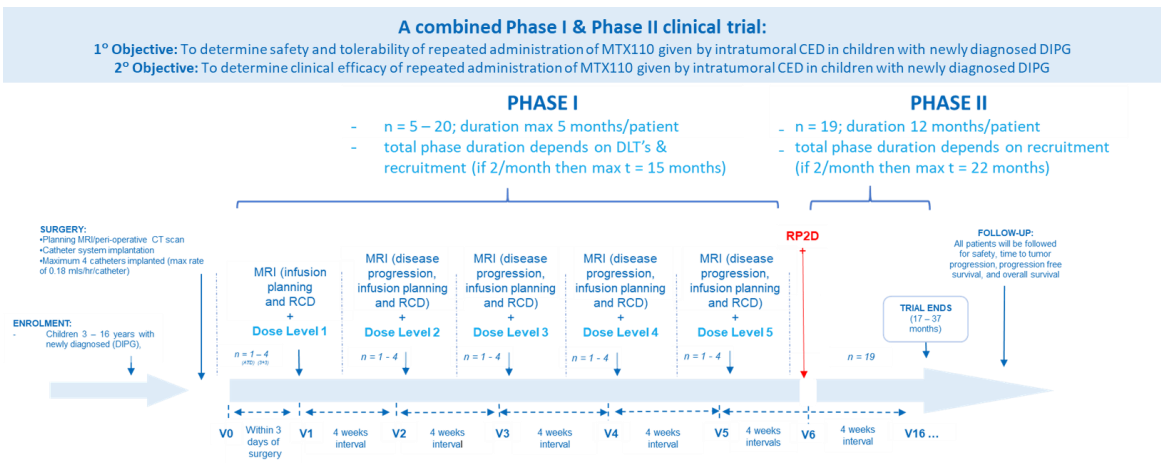
THE VALIDATION

Data (contd)

Animal studies conducted by Midatech in collaboration with UCSF similarly show encouraging efficacy data, where MTX110 prolongs survival in a patient-derived rat DIPG xenograft model when delivered by CED. A significantly (p=0.0372) improved survival difference was evidenced between control and MTX110 – 64 days for MTX110 versus 52 days for Control, even at a relatively low dose of 100uM. Toxicology safety data has established a large therapeutic window, with doses of up to 1000uM (and potentially higher) proven safe and being well tolerated *in vivo* despite highly potent in vitro IC50 efficacy of at concs less than 100nM. This suggests that the current dose can be increased at least 10 fold, with an even greater impact on survival. The current human dose is 30uM, again suggesting that this can similarly be safely increased 30 fold to 1000uM.



A first in human combined Phase I / II study is underway in DIPG, with a dose escalation phase followed by an efficacy phase at the recommended phase II dose (RP2D). The study commenced May 2018, and is progressing on track with patients tolerating therapy well.



Glioblastoma Multiforme (GBM)

MTX110 as a treatment for adult brain cancer GBM is in pre-clinical studies. Published data establishes that MTX110, up to a concentration of 30 µM, was safe and was distributed effectively in normal brain, and warrants further clinical investigation. The objective is to progress this program into clinic during the course of 2019/2020.

Journal of Neurosurgery: Pediatrics
September 2018 / Vol. 22 / No. 3 / Pages 288-296

The distribution, clearance, and brainstem toxicity of panobinostat administered by convection-enhanced delivery

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PARTNERING

MidaSolve™ is a nanoscale technology that solubilises chemotherapeutics to allow local delivery in liquid form directly into the tumour cells. MidaSolve™ products provide opportunities for Midatech to either develop internally or license to pharmaceutical partners. If you are interested to hear more and want to be part of this cutting edge healthcare science, contact …