SPINAL CORD AND PROPERTIES OF CEREBROSPINAL FLUID: OPTIONS FOR DRUG DELIVERY
WHY DO WE NEED TO KNOW ABOUT THE SPINAL CORD ANATOMY AND PROPERTIES OF CEREBROSPINAL FLUID?

• SMA therapeutics need to reach cells in the spinal cord (primary target tissue)

• It is difficult to reach the spinal cord tissue because it is protected by the blood brain barrier
  • The blood brain barrier protects the spinal cord by only allowing certain molecules to reach the spinal cord tissue from the blood

• Some drugs are able to cross the blood brain barrier

• For molecules that are unable to penetrate the blood brain barrier, direct delivery to the spinal cord is a possible alternative
SUMMARY OF ROUTES OF DRUG ADMINISTRATION THAT BYPASS THE BLOOD BRAIN BARRIER

- Drugs can be delivered directly into the central nervous system (CNS)
  - Spinal cord tissue: intraparenchymal delivery
  - Subarachnoid space filled with cerebrospinal fluid
    - Intrathecal delivery into the lumbar area
    - Intracerebroventricular delivery into ventricles of the brain

Direct delivery into the spinal cord

Delivery through cerebrospinal fluid

Intraparenchymal (slide 6)

Intrathecal (slides 7-9)

Intracerebroventricular (slide 11)
CNS ANATOMY: THE SPINAL CORD IS AN EXTENSION OF THE BRAIN

• The spinal cord is an extension of the brain, and together with the brain, forms the central nervous system (CNS)

• Surrounded by specialized bones comprising the spinal column or vertebral column

• Spinal nerves are named according to where they exit the spinal column but not the spinal cord

• Spinal cord is regionally organized:
  • The cervical region innervates the upper limbs
  • The lumbar region innervates the lower limbs

http://www.daviddarling.info/encyclopedia
THE SPINAL CORD IS ENTIRELY PROTECTED BY BONE

- Well-protected by the vertebral (spinal) column
- The vertebral column is made up of individual vertebrae
- The vertebrae are separated by tough intervertebral discs
- Nerves enter and exit the spinal cord through intervertebral foramina
- Vertebral foramen: space where the spinal cord resides

http://anatomy.med.umich.edu/modules/spinal_cord_module/spinalcord_01.html
• Spinal cord tissue (parenchyma) has two layers
  • Outer layer: white matter
    – myelin sheathed nerve fibers
  • Inner layer: gray matter
    – nerve cell bodies
• Intraparenchymal delivery is administration into the parenchyma (either white or gray matter)
SPINAL CORD TISSUE IS PROTECTED BY THREE MEMBRANES (MENINGES)

- **Dura mater**, outside layer

- **Arachnoid**, middle layer; comprises subarachnoid space, a drug delivery site

- **Pia mater**, innermost layer

*Cross-sectional representation of spinal cord protective membranes depicted on next slide*
THE SUBARACHNOID SPACE IS FILLED WITH CEREBROSPINAL FLUID (CSF)

Cross-sectional representation of spinal cord protective membranes

Subarachnoid space; filled with CSF

Spinal cord parenchyma

INTRATHECAL ROUTE OF ADMINISTRATION DELIVERS DRUGS INTO CSF OF THE SUBARACHNOID SPACE

- Spinal cord does not span the entire vertebral column and terminates at L1 vertebrae
- Intrathecal delivery at L3 avoids damaging the spinal cord
- Epidural injection is not the same as intrathecal delivery
DRUGS DELIVERED TO CSF CAN REACH THE BRAIN AND SPINAL CORD TISSUES

- Location of CSF
  - Subarachnoid space surrounding the brain and spinal cord
  - Central canal of the spinal cord
  - Brain ventricles
- Functions
  - Protection and buoyancy
  - Excretion of waste products
  - Transports hormones (endocrine medium of the brain)
- CSF is replaced several times a day and exchanges with the bloodstream
- CSF oscillates with the cardiac cycle, which provides constant mixing
- Volume (1/3 in the ventricles, 2/3 in subarachnoid space)
  - Newborns: 30-50 ml
  - Children: 65-100 ml
  - Adults: 90-150 ml

Lenninger et al, 2009
ICV ADMINISTRATION PROVIDES DELIVERY TO BOTH THE BRAIN AND THE SPINAL CORD

• Intracerebroventricular (ICV) delivery is administration into a brain ventricle
• Ventricles are 4 cavities within the brain where CSF is produced (400-500 ml per day)
• Ventricles are connected to the subarachnoid space of the brain and spinal cord

http://universe-review.ca/I10-80-ventricles.jpg
MOST DRUGS DELIVERED TO CSF REQUIRE REPEATED ADMINISTRATION

- CSF is absorbed into the bloodstream via two routes
  - Specialized capillary-filled structures in the brain (villi)
  - Capillaries of the subarachnoid space throughout the CNS
EACH DRUG MAY REQUIRE A SPECIFIC ROUTE TO ACHIEVE OPTIMAL RESULTS: OPTIONS FOR CNS DELIVERY

Direct delivery into the spinal cord

Delivery through cerebrospinal fluid

**Intraparenchymal:**
direct delivery to spinal cord tissue (white or gray matter)

**Intrathecal:**
delivery to spinal cord and brain; higher concentration in the spinal cord

**Intracerebroventricular:**
delivery to brain and spinal cord; higher concentration in the brain

To learn more about intrathecal delivery, go to [http://www.learnaboutsma.org/antisense/5.html](http://www.learnaboutsma.org/antisense/5.html)