Advances in Targeted Drug Delivery

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Intrathecal Baclofen Therapy

• Intrathecal administration eliminates systemic side effects

• Drug is dramatically more effective because it reaches target receptor sites

• Variety of dosing schedules available
  – Simple Continuous
  – Complex Dosing Patterns
Pharmacokinetics of Baclofen

**Oral**
- 60 mg dose: 0.024 mcg/mL IT lumbar concentration
- Half-life 3-4 hours

**Intrathecal**
- 600 mcg/day dose: 1.24 mcg/mL IT lumbar concentration
- Lumbar to cervical concentration is 4:1
- Half-life 4-5 hours
- Elimination by bulk CSF turnover
Synchronomed II ITB Pump

Old 18ml
New 20ml
MEDSTREAM Programmable Infusion System

- System consists of:
  - Programmable pump (20 or 40mL)
  - Control Unit
  - Catheter(s)
  - Misc. accessories (refill, bolus kits....)

- Indications:
  - Treatment of chronic intractable pain (benign or malignant)
  - Treatment of severe spasticity

- Approved intrathecal drugs:
  - Baclofen injection sterile solution (Spasticity)
Injection Therapy

- **Best effect:**
  - Localized spasticity;
  - Smaller muscles;
  - Small # of muscle groups;

- **Consider**
  - Early Intervention;
  - Combining with Intrathecal Baclofen Therapy.
Pharmacology of Botulinum Toxin

- 7 distinct antigenic types (serotypes):
  - A, B, C, D, E, F, G

- Serotypes differ
  - Biochemical structure and molecular weight
  - Potency (ED$_{50}$)
  - Intracellular target
TDD for Neurodegenerative diseases

Routes of Delivery:
- Intrathecal;
- Intracerebroventricular;
- Intraparenchymal

Purpose:
- Treatment;
- Prevention;
- Imaging.
<table>
<thead>
<tr>
<th>Chronic ICV Infusion System*</th>
<th>SynchroMed® II Infusion System</th>
<th>Ventricular Catheter Anchor*</th>
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<table>
<thead>
<tr>
<th>Acute Infusion Systems*</th>
<th>Paradigm® Veo</th>
<th>MANTIS*</th>
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*Products in Development / Investigational Use

Medtronic Infusion System Platforms*
Factors that can influence drug distribution in the CNS

<table>
<thead>
<tr>
<th>Micro</th>
<th>Macro</th>
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<tbody>
<tr>
<td><strong>Cell</strong></td>
<td><strong>Number of device outlets</strong></td>
</tr>
<tr>
<td>- Receptor#</td>
<td>- Flow distribution</td>
</tr>
<tr>
<td>- Association Rate</td>
<td>- Drug stability in device</td>
</tr>
<tr>
<td>- Disassociation Rate</td>
<td>- Surgical navigation</td>
</tr>
<tr>
<td>- Uptake rate</td>
<td>- Drug adhesion to catheter wall</td>
</tr>
<tr>
<td>- Efficacy Biomarker</td>
<td></td>
</tr>
<tr>
<td><strong>Matrix</strong></td>
<td><strong>3D Anatomy</strong></td>
</tr>
<tr>
<td>- Porosity</td>
<td>- Hydraulic Permeability</td>
</tr>
<tr>
<td>- Diffusion Coefficient</td>
<td>- Directionality (DTI)</td>
</tr>
<tr>
<td>- Bulk Clearance Rate</td>
<td>- Anatomical Structures</td>
</tr>
<tr>
<td>- Metabolic Rate</td>
<td>- Anatomical “discontinuities”</td>
</tr>
<tr>
<td>- Drug/solute viscosity</td>
<td>- Scaling to human anatomy</td>
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<td><strong>Whole System</strong></td>
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Anti-Amyloid Antibodies for Alzheimer’s Disease

- Route: Intraventricular delivery;
- Duration: Life long therapy;
- Purpose: Decrease of Amyloid burden;
- Clinical correlation: improvement of memory and cognitive function
## Anti-amyloid antibody for Alzheimer’s Disease

**Indication:** Mild to Moderate AD

**Therapy:** Disease Modifying

**Route:** Intracerebroventricular (ICV)

**Device:** SynchroMed Pump and ICV Catheter

**Drug:** MDT-8326 (Antibody) – Internal Project

**Refill Rate:** Every 30-60 days

**Duration:** Life-Long (chronic delivery)

**Desired Effects:**
- Decrease amyloid burden
- Improve memory
- Slow disease progression

**Stage of Development:** Preclinical – IND Enabling

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**Passive Immunotherapy**
Amyloid beta accumulates prior to clinical symptoms

**Figure 2: Dynamic biomarkers of the Alzheimer’s pathological cascade**

Aβ is identified by CSF Aβ₄₂ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

(Modified from Jack et al., 2010)
Superior efficacy and safety with ICV anti amyloid antibody compared to peripheral delivery

Intracerebroventricular amyloid-β antibodies reduce cerebral amyloid angiopathy and associated micro-hemorrhages in aged Tg2576 mice

Deopak R. Thukkeri, Murcy R. Watherspoon, Jonathan Harrison, Thomas E. Keene, Deanna S. Lane, William F. Kaemmerer, Gregory R. Stewart, and Usk L. Shaffer

Communicated by Richard L. Shizuru, Beth Israel Deaconess Medical Center, Boston, MA, January 16, 2008 (received for review October 10, 2008)

Although immunization against amyloid-β (Aβ) holds promise as a disease-modifying therapy for Alzheimer disease (AD), it is associated with an unacceptably accelerated rate of amyloid in the cerebrovascular system (i.e., cerebral amyloid angiopathy [CAA]) and a heightened risk of micro-hemorrhages. The central and peripheral mechanisms proposed to modulate amyloid with anti-Aβ immunotherapy remain largely elusive. Here, we compared the effects of prolonged intracerebroventricular (ICV) versus systemic delivery of anti-Aβ antibodies on the behavioral and pathological changes in an aged Tg2576 mouse model of AD. Prolonged ICV infusions of anti-Aβ antibodies dose-dependently reduced the parenchymal plaque burden, astrogliosis, and dextran-2-hemorrhage at doses 10- to 50-fold lower than used with systemic delivery of the same antibody. Both ICV and systemic anti-Aβ antibodies reversed the behavioral impairment in contextual fear conditioning. More importantly, unlike systemically delivered anti-Aβ antibodies that aggravated vascular pathology, ICV-delivered antibodies globally reduced CAA and associated micro-hemorrhages. We present data suggesting that the divergent effects of ICV-delivered anti-Aβ antibodies result from gradually engaging the local (i.e., central) mechanisms for amyloid clearance, distinct from the mechanisms engaged by high doses of anti-Aβ antibodies that circulate in the vasculature following systemic delivery. With robust efficacy in reversing AD-related pathology and an unprecedented benefit in reducing CAA and associated micro-hemorrhages, ICV-targeted passive immunotherapy offers a promising therapeutic approach for the long-term management of AD.

[Graphs and images showing plaque area comparisons between Systemic and ICV delivery across different brain regions (cerebral cortex and hippocampus).]
Extended PoC in non-human primate model demonstrates

**Delivery of drug where most needed**

- 50-fold higher drug conc in CSF

**Therapy engages Aβ target in CSF**

- Fractional clearance rate of Aβ (% of total)

**Efficacy**

- Aged Stump-tailed macaque model
  - Control (high plaque load)
  - Therapy (reduced plaque load)
  - Drug device therapy for 3 months

**Plaques in brain**

- % Plaque area
  - Control: n=4
  - Therapy: n=6
  - *
Recently completed phase I/II PD clinical trial with ICV infusion

- **Indication:** Late-stage PD unresponsive to or experience motor complications due to levodopa therapy
- **Delivery:** Intracerebroventricular (ICV) using Synchromed II pump and catheter
- **Duration:** Permanent implantation. Continuous delivery for 2 weeks followed by 3 month recovery period (Phase I)
- **Drug agent:** PDGF-BB
- **Desired effects:** Disease modifying therapy for Late-stage PD unresponsive to levodopa or suffer from motor complications of therapy.
- **Proposed MoA:** Neurogenesis. Proof of concept and NOAEL established in rodents and primates.
Recently completed phase I/II ALS clinical trial with ICV infusion

- **Indication:** ALS (spontaneous and familial)
- **Delivery:** Intracerebroventricular (ICV) using Synchromed II pump and catheter
- **Duration:** Continuous infusion
- **Drug agent:** rec human VEGF-165
- **Desired effects:** Prolong and improve quality of life
- **Proposed MoA:** Direct neurotrophic activity on motor neurons, enhance local oxygen delivery, improve general motor neuron and glial health. Proof of concept and NOAEL established in rodents and primates.

![Diagram of VEGF delivery and function](image)

**Function**
- Swallowing
- Eye movements
- Facial muscles
- Speech
- Breathing (diaphragm)
- Upper limb movement
- Muscles of back and abdomen
- Lower limb movement
- Bladder and sphincter function

Debbie Maizels
Overview of Huntington’s Disease

- Debilitating progressive neurological dyskinesia
- Onset of symptoms typically between 30 and 50 years
- Life expectancy around 20 years following onset of symptoms
- No disease modifying treatment currently available
Overview of Huntington’s Disease Therapy

• First genetic disorder discovered by genetic linkage (1993)
• Autosomal dominant genetic disorder – inherit one mutant gene copy and you will get the disease
• Simple genetic test for diagnosis
• Simple treatment strategy:

BLOCK MUTANT PROTEIN (mHTT)

PREVENT PROGRESSION OF DISEASE
Protein suppression for Huntington’s Disease

<table>
<thead>
<tr>
<th>Indication</th>
<th>Huntington’s Disease (HD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>Disease-Modifying</td>
</tr>
<tr>
<td>Route</td>
<td>Intraparenchymal (IPa)</td>
</tr>
<tr>
<td>Device</td>
<td>SynchroMed Pump with IPa Catheter</td>
</tr>
<tr>
<td>Drug</td>
<td>anti-huntingtin siRNA (Small Interfering Ribonucleic Acid)</td>
</tr>
<tr>
<td>Duration</td>
<td>Chronic Delivery. Refill pump every 30-90 days</td>
</tr>
</tbody>
</table>
| Desired Effects     | • Suppress mutant huntingtin protein expression  
|                     | • Improve Quality of Life  
|                     | • Slow disease progression  
|                     | • Prevent disease onset (prophylactic) |
| Stage of Development| Preclinical – IND Enabling |
RNA interference process

Target mRNA degradation

Targeted Gene Silencing

Natural Process of RNAi

mRNA degradation

Target Eliminated
HttsiRNA Suppresses Htt in the NHP Striatum
RNA targeting for neuromuscular disorders

- Myotonic Muscular dystrophy;
- Spinal muscular atrophy;
- Duchenne Muscular Dystrophy;
Therapy of RNA-Mediated Diseases

A) Short antisense oligonucleotide transcripts can eliminate the toxic RNA hairpin structure by RNAase H degradation of the toxic RNA or can interfere with the formation of the hairpin structure.

B) Small molecules can be used to interfere directly with the interaction between toxic RNA and its binding proteins.
Antisense Oligonucleotides

1. First-generation antisense oligonucleotides - short single-stranded oligodeoxynucleotides with complementary base pairing to mRNA target sequences - with RNase H-mediated degradation of target mRNA. Did not achieve high amounts to quickly suppress target genes or achieve prolonged high levels.

2. Modifications led to ASO competent for steric block applications; the phosphorothioate and phosphorodiamidate morpholino (PMO) variants. Function via direct sequence-specific steric block via hybridization to pre-mRNA to alter pre-mRNA splicing, or hybridization to mRNAs to prevent ribosome recruitment and block mRNA translation.

3. These ASO can modulate specific pre-mRNA splicing events, to inhibit specific mRNAs harboring mutations in non-coding elements of RNA (for example, 5′ or 3′ untranslated regions (UTRs)), or to block non-coding RNAs such as microRNAs.
Antisense Oligonucleotides & RNA Splicing in Neuromuscular Disease

- Myotonic Dystrophy- Pre-RNA hairpin loops sequester splicing factors altering protein expression- reversed by antisense oligonucleotides.


- Duchenne Muscular Dystrophy- Mutation causing deletions leading to truncated unstable dystrophin protein- reversed with exon skipping antisense oligonucleotides
Therapy with ASO and Small Molecules in Myotonic Dystrophy

- Using antisense targeting treatment at toxic mRNA level in animal models of DM1
  - Morpholino oligonucleotide made up of 8 CAG repeats block interaction of the expanded CUG repeat with MBNL1 in a mouse model of DM1- Wheeler et al
    - This morpholino led to elimination of RNA foci, corrected splicing abnormalities, and reversed clinical myotonia.
  - Modified ASO in 2 mouse models of DM1 also resolved RNA foci and splicing abnormalities, myotonia persisted-Mulders et al

- Small molecules
  - Pentamadine blocked the interaction of CUG repeats with MBNL1, reversing splicing defects in cell culture and in a mouse model of DM1-Warf et al.
ANTISENSE THERAPEUTICS: Systemic reawakening of a silent gene to improve survival in SMA

- Intracerebroventricular (i.c.v.) administration of antisense oligonucleotide, ASO-10-27, to newborn *Smn1*-deficient pups that were transgenic for *SMN2*, increases survival from 10 to 16 days. Passini et al. Sci Transl Med 2011
- The combination of systemic s.c. and i.c.v. administration of ASO-10-27 and increased survival to 108 days (s.c.) and 173 days (i.c.v. and s.c.)
- Higher doses of ASO increased survival to 248 days. Hua et al. Nature 2011.
- *SMN2* splicing changes induced by s.c. ASO-10-27 were noted in many tissues, including the CNS- possibly due to incomplete closure of the blood–brain barrier in neonates and/or retrograde transport in motor neurons
- Neonatal SMA mice had decreased circulating insulin-like growth factor 1, and ASO-10-27 restored IGF1 to normal levels. Thus, SMN important in peripheral tissues, including liver.
Antisense oligonucleotide-mediated splice-modulation of the human DMD gene- Splice-switching oligonucleotide.

A Normal

DMD patients

B Exon skipping

C Multi-exon skipping

D Exon skipping in critical regions

N-terminus
Actin-binding domain

Rod domain
Cys-rich domain

C-terminus
DAPC-binding domain
Antisense oligonucleotide
TDD for Imaging of the Neurodegenerative conditions
Dopamine Transporter Imaging in PD
**DaTscan (Ioflupane I 123 Injection) Indications**

- DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS)
- In these patients DaTscan may be used to help differentiate essential tremor (ET) from tremor due to PS
  - DaTscan cannot differentiate between different forms of PS (eg, PD, MSA, and PSP)
  - DaTscan is an adjunct to other diagnostic evaluations
  - The effectiveness of DaTscan as a screening or confirmatory test and for monitoring disease progression or response to therapy has not been established
Lower binding PD vs control and non-early vs early PD
Lower binding putamen vs caudate in PD, early PD and non-early PD
Lower binding contralateral vs ipsilateral in PD and non-early PD

SPECT and PET Imaging


PET: positron emission tomography
How Does DaTscan (Ioflupane I 123 Injection) Aid Diagnosis in Suspected PS?

Conserved striatal DaT activity

Marked reduction in striatal DaT activity

Images courtesy of Birmingham City Hospital, UK

DaT: dopamine transporter
**DaTscan (Ioflupane I 123 Injection) Mechanism of Action**

- DaTscan, ioflupane $^{123}$I, binds reversibly to human DaT
- Radiolabel concentrates in striatum (caudate nucleus and putamen)
- Striatal binding selective and specific for presynaptic DaT
  - Abolished in presence of dopamine reuptake inhibitors
  - Unaffected by inhibitors of serotonin/norepinephrine reuptake
  - Visualized by SPECT imaging

DaT: dopamine transporter
DaTscan (Ioflupane I 123 Injection) Baseline Imaging Agreement With 36-Month Clinical Diagnosis

<table>
<thead>
<tr>
<th>Reader</th>
<th>n</th>
<th>Positive % agreement(^a) (95% CI) [% patients with an abnormal DaTscan image among patients with PS(^c)]</th>
<th>Negative % agreement(^b) (95% CI) [% patients with a normal DaTscan image among patients with non-PS(^c)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader A</td>
<td>99</td>
<td>77 (66, 87)</td>
<td>96 (82, 100)</td>
</tr>
<tr>
<td>Reader B</td>
<td>96</td>
<td>78 (66, 87)</td>
<td>96 (82, 100)</td>
</tr>
<tr>
<td>Reader C</td>
<td>98</td>
<td>79 (67, 87)</td>
<td>96 (82, 100)</td>
</tr>
</tbody>
</table>

\(^a\) Percentage of patients with abnormal DaTscan image among all patients with a clinical diagnostic reference standard of PS.

\(^b\) Percentage of patients with normal DaTscan image among patients with a non-PS clinical diagnostic reference standard.

\(^c\) Reference clinical diagnostic standard established by consensus panel evaluating data inclusive through 36 months of follow-up.

DaTscan™ prescribing information, 2011.
## Interpreting DaTscan (Ioflupane I 123 Injection) Images

<table>
<thead>
<tr>
<th>Normal</th>
<th>Examples of Abnormal DaTscan Images</th>
</tr>
</thead>
</table>

![Normal Image](image1.png) ![Abnormal Image1](image2.png)

![Normal Image2](image3.png) ![Abnormal Image2](image4.png)

![Normal Image3](image5.png) ![Abnormal Image3](image6.png)

![Normal Image4](image7.png) ![Abnormal Image4](image8.png)

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DaTscan™ prescribing information, 2011
Amyloid Imaging
development
Using imaging as a biomarker of brain pathophysiology of AD

R Buckner, J Neuroscience, 2005
**Imaging protocols:** Vary between compounds.  
Injection, 50-90 minutes uptake time, 10-20min scans

**18F Amyloid Imaging Compounds**

- **Fluorescent Stilbene:** X-34
  - **SB-13**
  - **18F-AV-1 (BAY 94-9172)**
  - **18F-AV-45**

- **Neutral Thioflavin Derivatives**
  - **11C-PIB**
  - **18F-PIB**

- **Florbetaben**
  - Bayer/Piramel
  - **18F-AV-1 (BAY 94-9172)**

- **Florbetapir**
  - (Amyvid)
  - Lilly
  - **18F-AV-45**

- **18F-Flutametamol**
  - GE

- **NAV 4694**
  - Piridinyl Benzofuran
  - Navidea
F18 Amyloid Imaging Tracers

Amyvid PET

- Biomarker-based diagnostic assessment:
  - Amyloid PET (Positive)