celerion

Translating Science to Medicine

Workshop #2: Accelerating Peptides into Human Studies: Drug Development and Regulatory Considerations

February 21, 2017

Agenda

8:00-8:15a	Introductions	
8:15-9:00a	Manufacturing and synthesis of peptide API's, discovery to early GMP. Latest trends in specifications	Robert Hagopian
9:00-9:45a	Basic formulation strategies to support nonclinical toxicity and human studies	Chris Rhodes
9:45-10:15a	Break	
10:15-11:00a	Regulatory considerations on peptide drug development and update on US review process	Duu-Gong Wu
11:00-11:45a	Drug development considerations for peptide therapeutics: pharmacokinetics and toxicology	Bruce Morimoto
11:45-12:00p	Wrap Up and Question & Answer	

Course Instructors

Robert Hagopian, MSc, MBA

Director of Business Development
PolyPeptide Laboratories, San Diego
Robert.Hagopian@polypeptide.com

- Bachelor of Science, Chemistry (UCLA)
- Masters, Organic Chemistry (UC San Diego)
- MBA, Marketing (San Diego State University)

celerion

Chris A. Rhodes, PhD

President & CEO
Drug Delivery Experts
crhodes@drugdeliveryexperts.com

- Bachelor of Science, Chemistry (New York University)
- PhD, Physical Organic Chemistry (UCLA)
- Postdoctoral Fellow (Yale University)

celerion

Duu-Gong Wu, PhD

Director of Regulatory Consulting, PPD
Former Deputy Director, New Drug Chemistry, FDA
Duu-Gong.Wu@ppdi.com

- MSc, Biochemistry (National Taiwan University)
- PhD, Biochemistry & Molecular Biology (University of Maryland)
- Postdoctoral fellow (Johns Hopkins University School of Medicine)

celerion

Bruce H. Morimoto, PhD

Vice President, Scientific Affairs

Celerion, Inc.

Bruce.Morimoto@celerion.com

- Bachelor of Science, Biochemistry (UCLA)
- PhD, Biochemistry (UCLA)
- Postdoctoral Fellow (UC Berkeley)
- Professor of Chemistry (Purdue University)

celerion

Drug Development Considerations: Pharmacokinetics and Toxicology

Points to consider

- Clinical indication
  - Life threatening
  - Unmet medical need (other treatment options?)
- Patient population
  - Comorbidities
  - Concomitant medications
- Dose, duration of treatment, route and frequency of administration

ICH Guidance

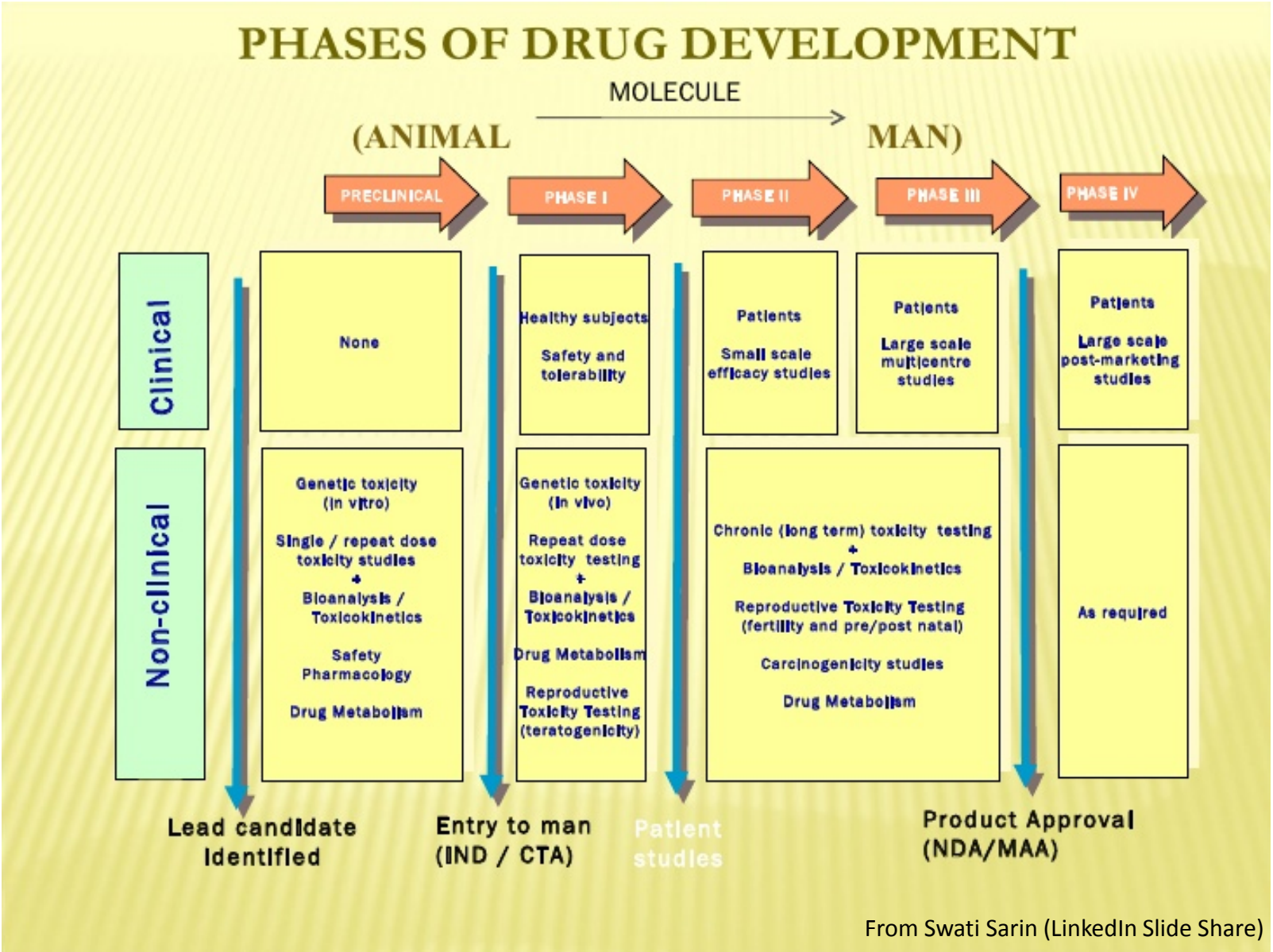
- S1A-C Carcinogenicity
- S2(R1) Genotoxicity
- S3A-B Pharmacokinetics-toxicokinetics
- S4 Toxicity testing
- S5(R2) Reproductive toxicology
- S6(R1) Biotechnology products
- S7A-B Safety Pharmacology
- S8 Immunotoxicology
- S9 Nonclinical anticancer
- S10 Photosafety evaluation
- S11 Nonclinical pediatric testing

- M3(R2) Nonclinical safety studies for human trials

Types of studies conducted

- Dose-range finding (typically non-GLP)
  - Exploratory toxicity
- Acute, single dose toxicology
- Repeat dose toxicology
  - Duration needs to match or exceed intended clinical duration
- Safety pharmacology
- Genotoxicity
- Carcinogenicity
- Reproductive & developmental toxicology

When various studies done?



From Swati Sarin (LinkedIn Slide Share)

Classes of peptides

- Unmodified (“naked”), natural amino acids
- Modified peptides
  - Unnatural amino acids
  - Altered peptide bonds
  - Constrained (stapled, cyclic)
  - Peptidomimetics
- Conjugated
  - Glycosylation
  - PEGylation
  - Lipidation
  - Cell-penetrating peptides
- Complex formulations
  - Liposomes
  - Nanoparticles

Properties of Peptide Drugs

Pharmacokinetics & Metabolism Considerations

- Not often oxidative metabolized (Cytochrome P450s)
  - Low potential for drug-drug interactions
- Degraded primarily by proteases
  - Can have short plasma half-life

Safety Pharmacology & Toxicology Considerations

- Potent and target selective
  - Low potential for off-target interactions
- Potential for immunogenicity
- Larger molecular weight (typically > 500 Daltons)
- Polar chemical structure (nature of the peptide bond)

Peptide-selective considerations

Generally non-toxic

- Challenge to define the maximum tolerated dose (MTD)
  - Regulatory agencies want to understand dose and target organ toxicity
  - Multiples of the intended clinical dose not usually sufficient
- Maximum feasible dose (MFD)
  - Justify the high dose tested
  - MFD defined by solubility and volume of administration
    - Volume of administration dependent on species and route of administration
- Injection site reactions
- Genotoxicity. Generally not an issue with peptides unless non-natural sequences, conjugates

Immunotoxicity

- Similar consideration as to proteins
  - Immunosuppression
  - Immunogenicity
- Anti-drug (peptide) antibodies
  - Peptides often difficult to induce antibodies to
  - Watch for antibodies to excipients & carriers

Local tolerance

- Observation during *in vivo* pharmacology studies and repeat-dose studies
- Standard evaluation of site of administration
  - Signs of local irritation and histopathological evaluation
- Intranasal
  - Nasal cavity (not standard)
  - Olfactory lobes of brain
- Respiratory
  - Nasal cavity
  - Epiglottis
  - Respiratory tree

IND-enabling toxicology program

Objectives

- Understand adverse pharmacology
- Determine target organs for toxicity
- Assess reversibility of toxicity
- Provide information for human risk assessment
  - What are the expected dose-limiting toxicities?
  - What should the starting human dose be?
  - Guidance on clinical dose escalation?

Components of an IND-enabling tox program

- Safety pharmacology
  - CNS assessment (Irwin, Functional Observational Battery)
  - Cardiovascular (hERG inhibition, ECG evaluation)
  - Respiratory (respiratory rate, tidal volume)
- Dose-range finding tox (non-GLP)
  - Single- and repeat-dose
  - Clinical signs & symptoms, clinical chemistry & hematology
  - Two species: rodent & non-rodent

GLP-tox studies

- Acute (single-dose)
- Repeat-dose (14-day minimum, duration of dosing to cover Phase 1 clinical duration)
  - Include recovery group (reversibility?)
  - Include toxicokinetics (satellite group for rodent)
- Reproductive tox
  - Needed for inclusion of females in clinical studies
  - US: women of child-bearing potential can be on contraception
  - Europe: repro tox required for testing in women

Outcomes

- Maximum Tolerated Dose (MTD)
  - Highest dose that does not cause unacceptable adverse events
    - Mortality: 10-15% at MTD
    - Body weight changes <10-15% at MTD
    - Histopathology: identify target organs
- No Observed Adverse Effect Level (NOAEL)
  - Dose (or drug exposure) which does not result in any adverse finding (clinical chemistry, hematology, pathology)

Design considerations

- Often 3 dose groups plus controls
  - High-dose. Produce some toxicity
  - Mid-dose. NOAEL?
  - Low-dose. Similar exposure to anticipated clinical dose
- Vehicle control
  - Formulation without active peptide
  - Peptides often in complex formulations, need to test excipients (especially true if novel excipients)

Case Study: Davunetide

Davunetide

- Smallest active fragment of Activity-Dependent Neuroprotective Protein (ADNP)

NAPVSIPQ

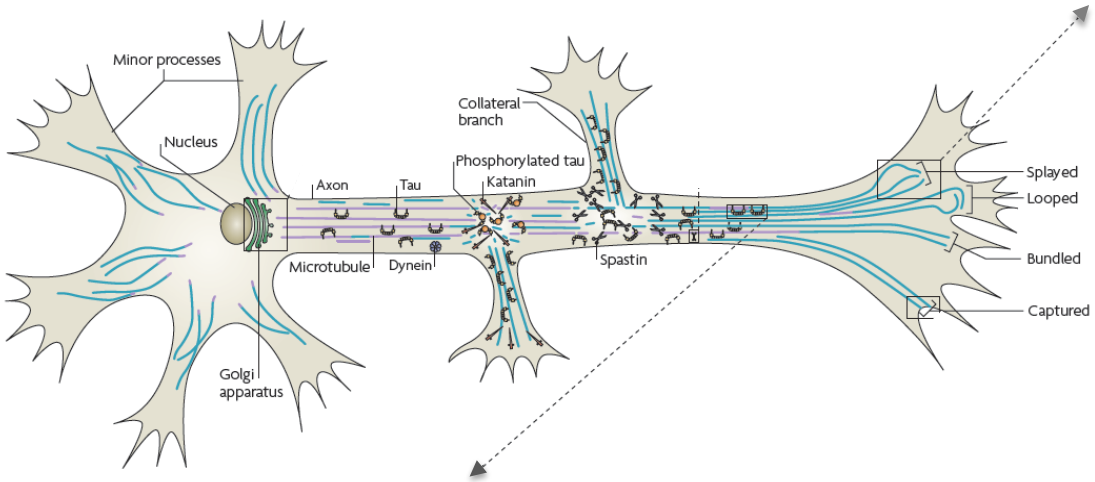
- Eight amino acid peptide
- Both intravenous and intranasal development programs

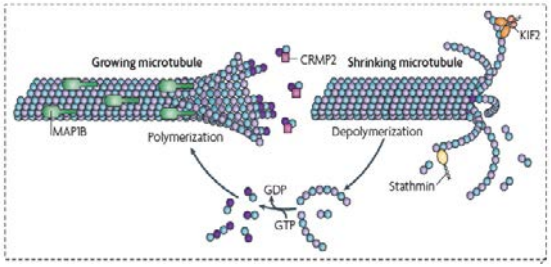
J. Neurochem. 1999; 72, 1283-1293
J. Mol. Neurosci. 2004; 24, 181-187
CNS Drug Rev. 2005;11(4):353-68. Review.

celerion

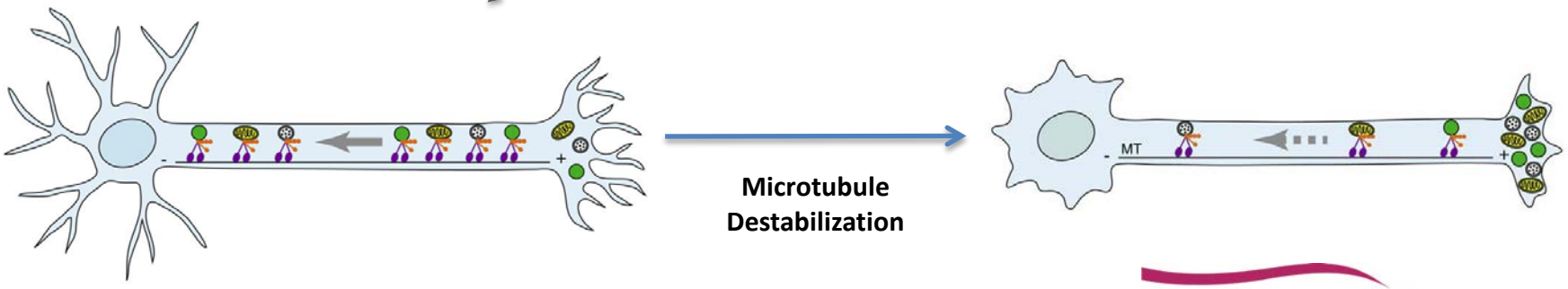
Mechanism of Action

- Microtubules essential for neuronal structure & function
- Destabilization occurs in many neurodegenerative diseases





Conde & Caceres, *Nat Rev Neurosci* 2009: 10; 319-332

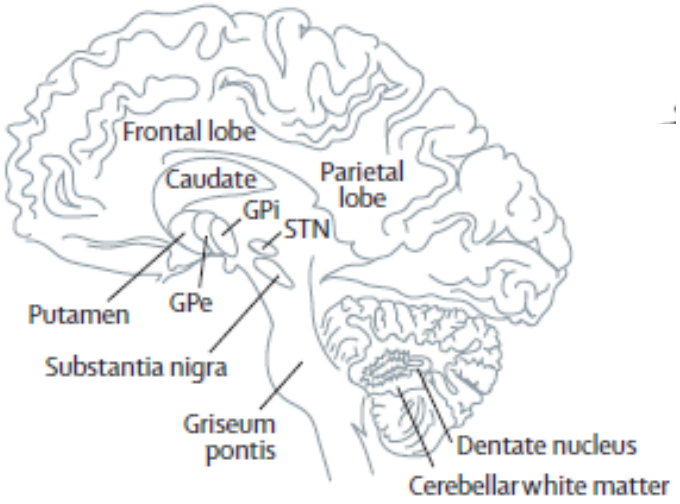


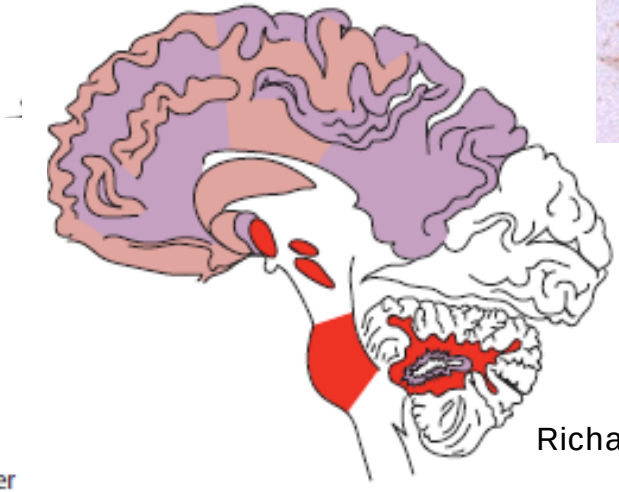
Perlson, et al. *TINS* 2010: 33; 335-344

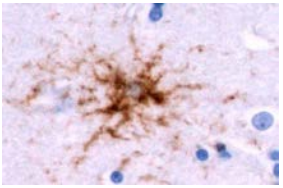
celerion

Progressive Supranuclear Palsy (PSP)

- A degenerative disease involving the brain stem, basal ganglia, cerebellum
- Clinical symptoms (movement problems, cognitive impairment) apparent result of the underlying tau pathology in the brain region controlling those functions







Richardson's Syndrome

Steele JC, Richardson JC, Olszewski J. 1964 Arch Neurol;10: 333–59.

Williams and Lees; *Lancet Neurol* 2009; 8: 270–79

Davunetide: Translation to PSP

Animal pharmacology

- Davunetide is active in relevant models of tauopathy
  - Impact on cognition/behaviour correlates with positive impact on tau pathology
- Davunetide is disease-modifying in preclinical models
  - Wide-ranging activity in models of neurodegeneration
  - Reduces neuronal loss and impacts underlying pathology

Clinical rationale

- PSP is a neurodegenerative tauopathy which manifests itself as akinesia/rigidity and cognitive dysfunction
- Intranasal route-of-administration
  - PSP patients: dysphagia (difficulty swallowing)
  - Twice daily (BID) dosing

Acute toxicology program

- Primary pharmacology studies done in rodent
  - Wide dose-range
  - No observed toxicities
- GLP-acute tox done only in dog

Species/ Strain	Method of Administration (Vehicle/Formulation)	Doses	Gender and No. per Group	No Observed Effect Level (NOEL)	Noteworthy Findings	Study Number
Dog/ beagle	Intravenous Sodium Chloride for Injection USP Intranasal Sodium Chloride for Injection USP	0, 5, 50, 500 mg/kg 500 mg	3 M	500 mg/kg 500 mg	No deaths. No test article related signs of toxicity	MPI Research 855-031

celerion

Safety pharmacology studies

- Standard ICH S7A and S7B battery
  - GLP-compliant
  - Intravenous route-of-administration to maximize drug exposure

Organ System Evaluated	Species/ Strain	Route of Administration	Doses	Gender& #/Group	Noteworthy Findings	GLP Compliant	Study Number
Central Nervous System	Rat/ SD	Intravenous Sodium Chloride USP	0, 1, 10, 100 mg/kg	10 M 10 F	No deaths, clinical signs, or effects on qualitative, quantitative or motor activity assessment.	Yes	MPI Research 855-037
Cardiovascular	Dog/ beagle	Intravenous Sodium Chloride USP	0, 1, 10, 100 mg/kg	3 M 4 F	No deaths. No clinical signs or changes in body weight or body temperature. No effects on blood pressure. No changes in ECG, including PR, RR QT, or QRS intervals.	Yes	MPI Research 855-038
Respiratory	Dog/ beagle	Intravenous Sodium Chloride USP	0, 1, 10, 100 mg/kg	3 M 4 F	No deaths or clinical signs. No effects on respiratory parameters (respiratory rate, tidal volumen, or minute volume).	Yes	MPI Research 855-038

IND-opening repeat dose tox studies

Species/ Strain	Method of Administration	Doses	Frequency & Duration	Gender and No. per Group	No Observed Effect Level (NOEL)	Noteworthy Findings	Study Number
Rat/ CD	Intranasal[a]	0, 1, 10, 40 mg/day	14-day	5 M	40 mg/day	There was no mortality, clinical signs nor changes to body weight, food consumption, hematology, coagulation, clinical chemistry parameters or gross pathology.	MPI Research 732-021
Rat/ CD	Intranasal[b]	0, 0.2, 2, 10, 100, 1000 mg/day	30-day	10 M 10 F	1000 mg/day	There was no mortality, clinical signs nor changes to body weight, food consumption, hematology, coagulation, clinical chemistry parameters or gross and microscopic pathology.	MPI Research 855-002
Dog/ Beagle	Intranasal[b]	0, 2, 14, 140, 1400/925 mg/kg/day	30-day	4 M 4 F	925 mg/day	There was no mortality, clinical signs nor changes to body weight, food consumption, hematology, coagulation, clinical chemistry parameters or gross and microscopic pathology.	MPI Research 855-003
Notes:							

[a] Nasal Formulation: 5% Sefsol (1-monocapryloyl-rac-glycerol), 20% isopropanol in water
[b] Nasal Formulation: Per 1 mL sterile water USP, 7.5 mg sodium chloride, 1.7 mg citric acid monohydrate, 3.0 mg disodium phosphate dihydrate, 0.2 mg benzalkonium chloride solution (50%)

celerion

Integrated safety summary & starting dose

Species	Study	NOAEL (µg/day)	NOAEL (mg/kg)	NOAEL (body surface area)	HED (mg/kg)
Rat	30-day tox	1000	3.2 mg/kg	19.2 mg/m^2	0.52 mg/kg
Dog	Acute tox	500	50 mg/kg	300 mg/m^2	8.1 mg/kg
Dog	30-day tox	925	0.9 mg/kg	18 mg/m^2	0.49 mg/kg

Dose (mg)	Dose for 50 kg subject (mg/kg)	Dose (mg/m^2) by body surface area[1]	Safety Factor[2]	Percent of HED Based on Nonclinical NOEL
1	0.02	0.74	24.3	4%
3	0.06	2.22	8.1	12%
10	0.20	7.40	2.4	41%
12.5	0.25	9.25	2.0	51%
15	0.30	11.10	1.6	62%

[1] Dose by body surface area = dose (mg/kg) x 37 or dose (mg)/1.73 m^2

[2] Safety factor calculated using the NOEL converted to body surface area from the 30-day dog toxicity study (18 mg/m^2). Body surface area for dog is 0.4 m^2

Summary

- Did not identify a MTD by intranasal route of administration
- Needed to define the maximum feasible dose
  - Pharmacokinetic argument
  - Nasal solution at solubility limit
  - Escalate volume of administration
  - Dose multiple times within 1 min
  - Looked at exposure and variability as function of volume administered
- Used IV drug exposure along with MFD intranasal tox to justify clinical use

References

- Heidel SM, Page TJ. Current practices in the preclinical safety assessment of peptides. In: Preclinical safety evaluation of biopharmaceuticals: a science-based approach to facilitating clinical trials (ed: Cavagnaro, JA). John Wiley & Sons, 2013
- Vugmeyster Y, Theil F-P, Khawli L, Leach MW. Pharmacokinetics and toxicology of therapeutic proteins: advances and challenges. *World J Biol Chem.* 3(4), 73-92, 2012
- Morimoto BH, Fox AW, Stewart AJ, Gold M. Davunetide: a review of safety and efficacy data with a focus on neurodegenerative diseases. *Exp Rev Clin Pharmacol* 6(5), 483-502, 2013

celerion

Questions?

bruce.morimoto@celerion.com