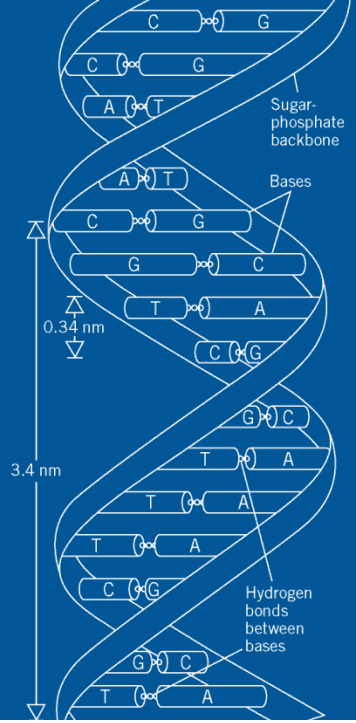

Should Biologics be Evaluated in Preclinical Abuse Liability Studies?

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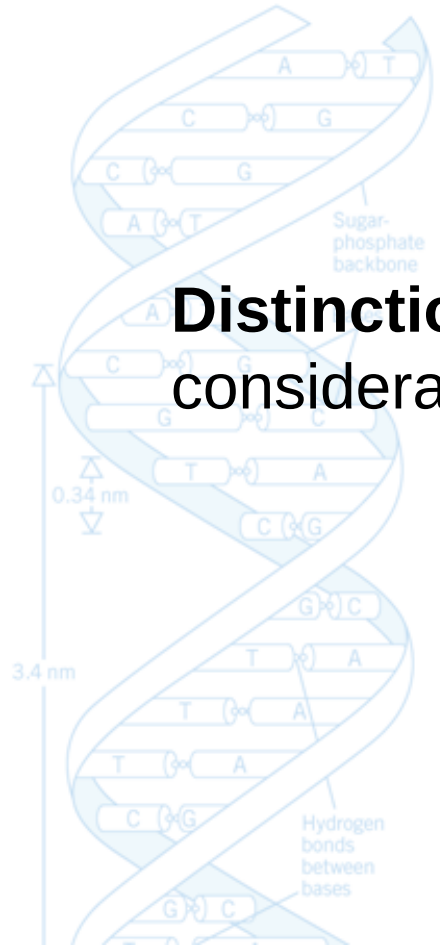
Senior Scientist, Safety Assessment
Genentech, Inc.

Acknowledgements

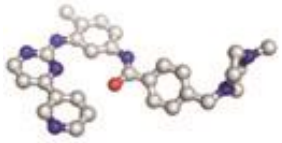
- Carrie Markgraf and David Compton – co-leads, Preclinical Abuse Liability subgroup of the Cross-Company Abuse Liability Consortium (CCALC)
- Members of the PAL
- Jessica Couch, Genentech Safety Assessment Neuroscience Expert Working Group leader
- Janel Boyce-Rustay, Genentech Product Development Regulatory



Distinctions between small and large molecules – considerations for abuse liability testing

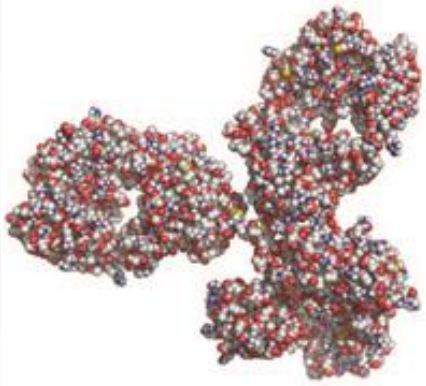
Characteristics of small molecule versus large molecule drugs

Characteristic	Small Molecule Drugs	Biologics
Production	Chemically synthesized	Produced by a host cell
Size	Low molecular weight	High molecular weight
Physicochemical properties	Well defined, stable	Complex • May be sensitive to heat, light, other stressors • May possess additional functionality (i.e. effector function)
	High tissue/cell permeability	Low tissue/cell permeability
PK properties	Oral bioavailability, may be administered via different routes	Typically administered parenterally (IV/SC)
	May be metabolized to active intermediate(s)	Catabolized to amino acids
	Short $T_{1/2}$	Long $T_{1/2}$
Toxicity	Organ-specific toxicity	Receptor-mediated toxicity (exaggerated pharmacology)



small molecule
(imatinib)

< 1000 Da



monoclonal antibody

150 kDa

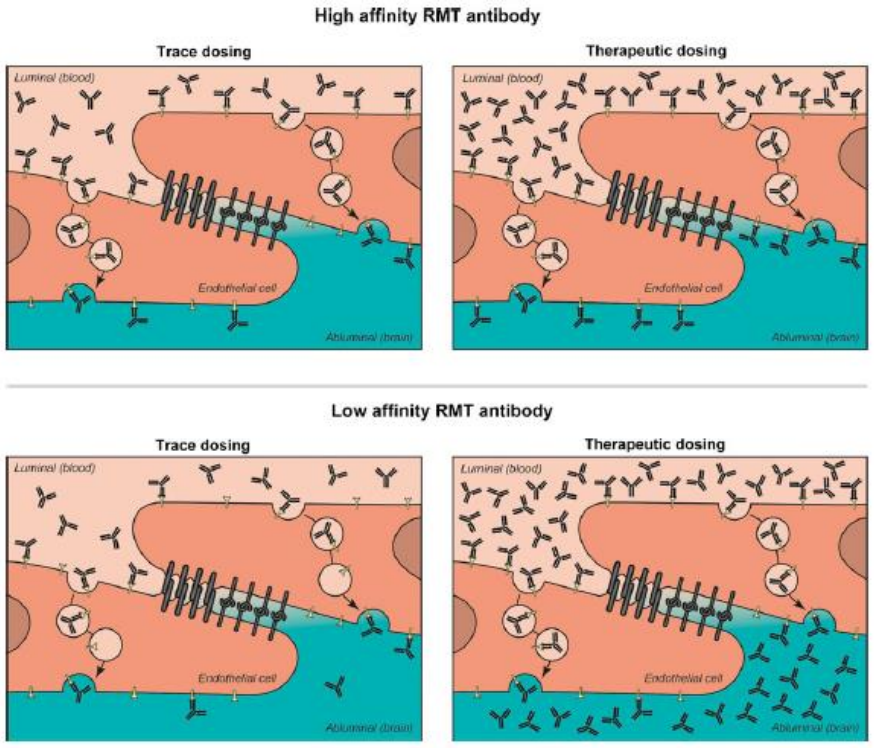
Considerations for Abuse Liability testing
Determining cause for concern – Brain penetration

- Is a candidate molecule CNS active?
  - Small molecule drugs mainly access the brain by diffusion
    - High lipophilicity, small size (molecular weight), and neutral charge
  - Large molecule drugs are effectively blocked from accessing the brain by the BBB
    - Concentrations of therapeutic antibodies reaching the brain are ~0.01 – 0.35% of peripheral (plasma) concentration
      - Note: disease states which compromise the BBB may permit increased transfer

<u>Consideration #1</u>: Brain penetration
Small molecules – a clear need for AL testing
Large molecules – questionable need for AL testing

Overcoming the challenge of the BBB
Using receptor mediated transport to get mAbs to the brain

- Progress in the development of bispecific antibodies targeted to brain transporters to facilitate entry

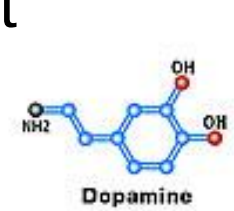


Yu and Watts, 2013

- Increased brain penetration of mAbs will prompt reconsideration of need for abuse liability studies

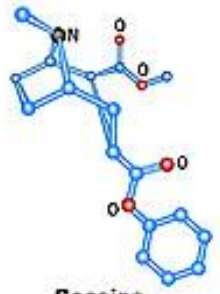
Considerations for Abuse Liability testing
Determining cause for concern – Target specificity

- Small molecules, or metabolites, may target receptors/transporters directly or indirectly
  - They may be structurally similar to endogenous ligands



Dopamine

Ritalin



Cocaine

- Large molecules, mAbs in particular, have exquisite target specificity and little off-target binding
  - With few exceptions, large molecules are not expected to bind to CNS receptors/channels

<u>Consideration #2</u>: Target specificity
Small molecules – a clear need for AL testing
Large molecules – questionable need for AL testing, consider on a case-by-case basis

Considerations for Abuse Liability testing
Determining cause for concern – Route/physchem properties

- By virtue of their physicochemical attributes, small molecules can be formulated for oral delivery
  - Stable at room temperature, can be absorbed from the gut and distribute efficiently to site(s) of action
  - Easily stored and distributed, and can be tampered with to facilitate non-medical use
- Owing to their physicochemical attributes, large molecules typically must be delivered via parenteral administration
  - Sensitive to changes in storage conditions, formulations designed to protect therapeutic protein
  - Catabolized readily, need to be injected IV or SC to facilitate delivery to site(s) of action (targets typically soluble (in circulation) or cell surface-expressed)
  - Cannot be easily stored/distributed, and tampering is likely to diminish efficacy
    - Distribution controlled by hospitals/pharmacies, cost is prohibitive

Considerations for Abuse Liability testing
Determining cause for concern – Route/physchem properties

- By virtue of their physicochemical attributes, small molecules can be formulated for oral delivery
  - Stable at room temperature, can be absorbed from the gut and distribute efficiently to site(s) of action
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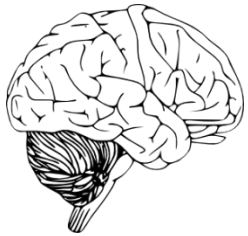
  - Distribution controlled by hospitals/pharmacies, cost is prohibitive

Consideration #3: Route/physicochemical properties
Small molecules – a clear need for AL testing
Large molecules – questionable need for AL testing

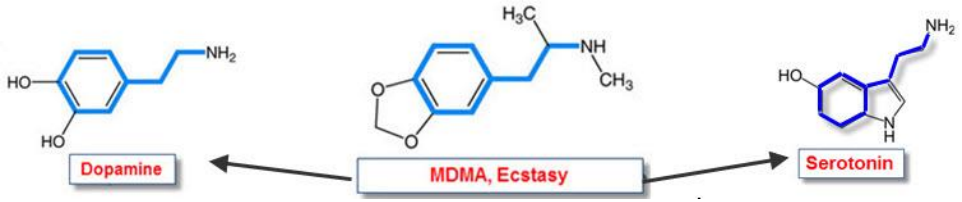
Considerations for Abuse Liability testing

Determining cause for concern – overall assessment

Consideration #1: Brain penetration



Consideration #2: Target specificity



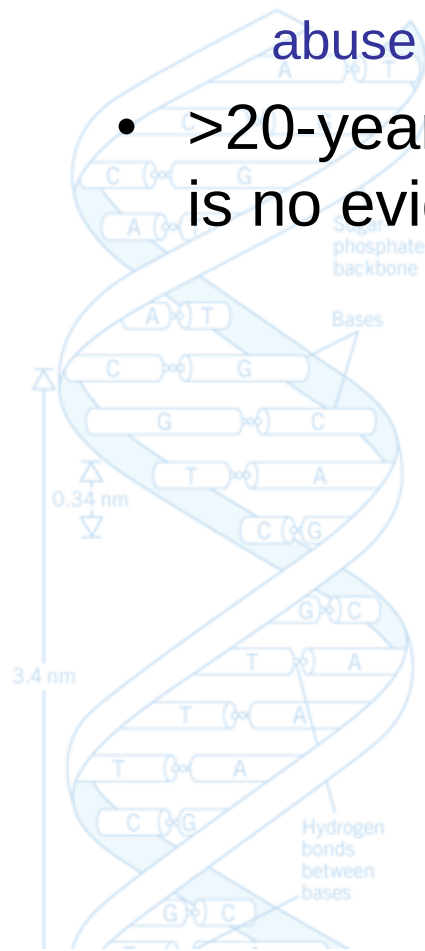
Consideration #3: Route/physchem properties

The aggregate of these factors determines the cause for concern

Small molecule generally >>> large molecule

A note on biologics history

- FDA approvals of monoclonal antibody drugs:
  - 2011 – present: 13, plus 5 currently under review
  - 1994 – 2010: 23, plus 5 withdrawals (for causes unrelated to abuse potential)
- >20-year history with >35 mAb products for which there is no evidence of abuse



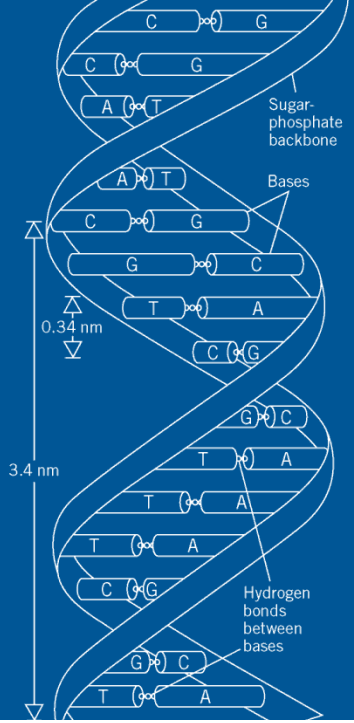
Example mAb abuse liability assessment
Accepted by FDA at EOPII meeting

- Target: brain-expressed protein, not neurotransmitter-related
- Effects from nonclinical studies: no evidence of sedative, stimulant, opioid, hallucinogenic, or cannabinoid-like behavioral effects in any in vivo animal studies
- PK: typical mAb half life
  - $T_{1/2}$ cynomolgus monkey = 16 – 23 days
  - $T_{1/2}$ human = 17 – 26 days
- Effects from clinical trials:
  - No imbalances in psychiatric AEs
  - No reports of withdrawal

Based on the very low likelihood of abuse potential related to the MOA of the drug and the known biology of the target, and the lack of nonclinical or clinical evidence to suggest abuse liability, the Sponsor does not believe that nonclinical or clinical AL studies are needed

Summary

- Abuse liability studies with large molecule drugs must be carefully considered
  - Brain penetrance is limited
  - Pharmacokinetics do not favor abuse potential (i.e. long $T_{1/2}$)
  - Target specificity is high and metabolism does not produce active intermediates – low risk of off-target effects
  - Physicochemical attributes impact stability and influence route of administration
  - All of these attributes may limit the utility of *in vitro and in vivo* abuse liability assays, as well as human abuse potential
- Guidance documents define expectations, but important considerations must be taken into account depending on molecule class
- A case-by-case approach should be employed and feedback sought from health authorities



Abuse Liability Assessment of Biologics – Further Considerations

Thomas Hudzik, PhD
Research Fellow
AbbVie – Preclinical Safety

No evidence for abuse potential nor liability, but potentially CNS-mediated effects

- Interferons
  - ~25% incidence of depression-like symptoms
- Pharmapendium™ search (FDA/EMEA Labels) of all biologics (vaccines, recombinant proteins, mAbs). N=150
  - Excluded reproductive and metabolic hormones and anabolics
- Comprehensive list of neuropsychiatric AEs (~200)
  - Exclusions due to probability of peripheral origin (eg., syncope), suicidal ideation, somnolence, convulsion of known origin (e.g., febrile), dementia, non-hallucinatory sensory disturbances.
- Sorted into 7 main categories

Terms with Hits by Category

Coordination/Speech
Aphasia
Balance disorder
Cerebellar ataxia

Consciousness
Coma
Altered state of consciousness
Depressed level of consciousness
Sedation

Mood
Depressed mood
Depression
Mood altered
Euphoric mood

Cognition
Amnesia
Amnestic disorder
Cognitive disorder
Confusional state
Disorientation
Disturbance in attention
Global amnesia
Memory impairment
Mental impairment
Thinking abnormal

Suicide
Completed suicide
Suicide attempt
Depression suicidal

Convulsion
Clonus
Complex partial seizures
Grand mal convulsion
Myoclonus
Simple partial seizures
Status epilepticus
Tonic clonic movements
Tonic convulsion

Hallucination
Hallucination
Depersonalization

Results of query

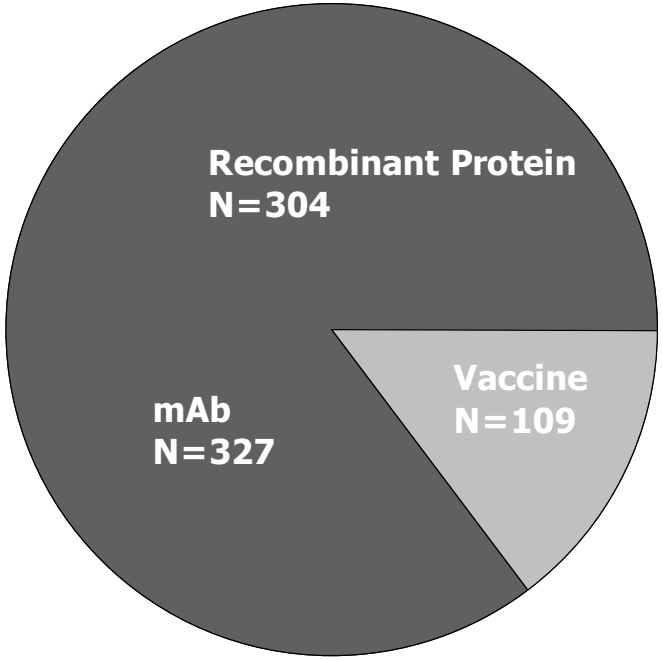
- 58 of 150 (40%) products had mention of 2 or more neuropsychiatric AEs in approval doc/label
- 15 recombinant protein, 25 mAb, 17 vaccine
- 740 AE mentions across different dose levels and formulations of these products

Caveats

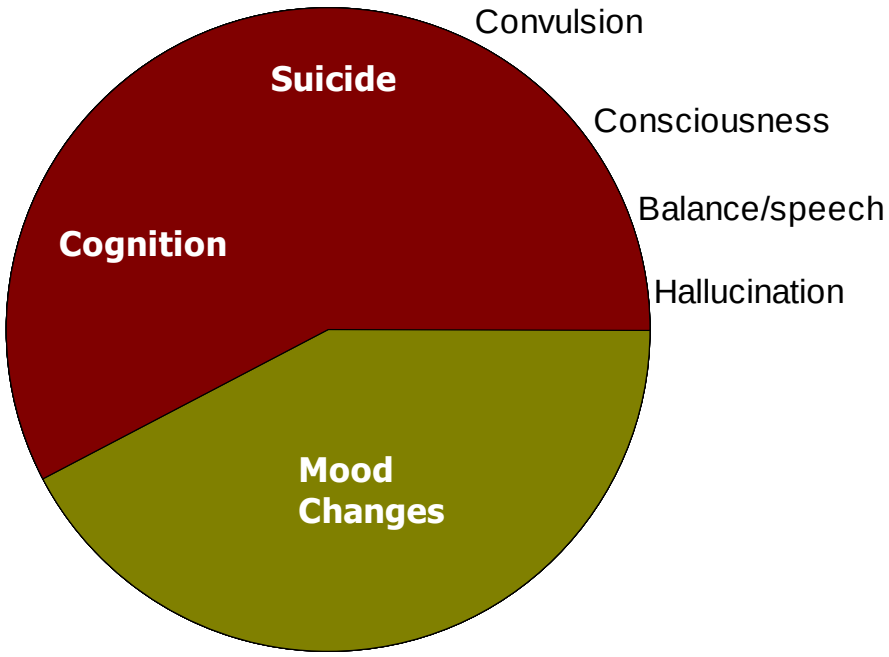
- No data on population frequencies for AE
- Unclear strength of association of AE to disease vs treatment, or interaction of disease with treatment

Results, continued

Frequency



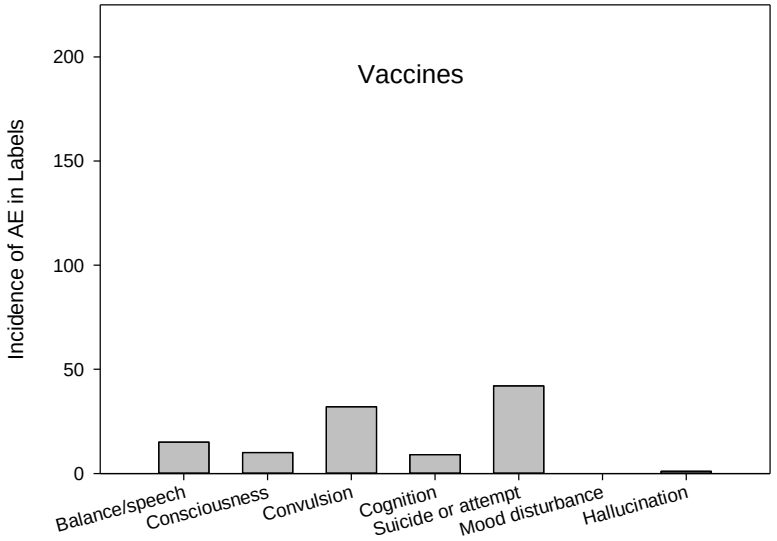
% of Total



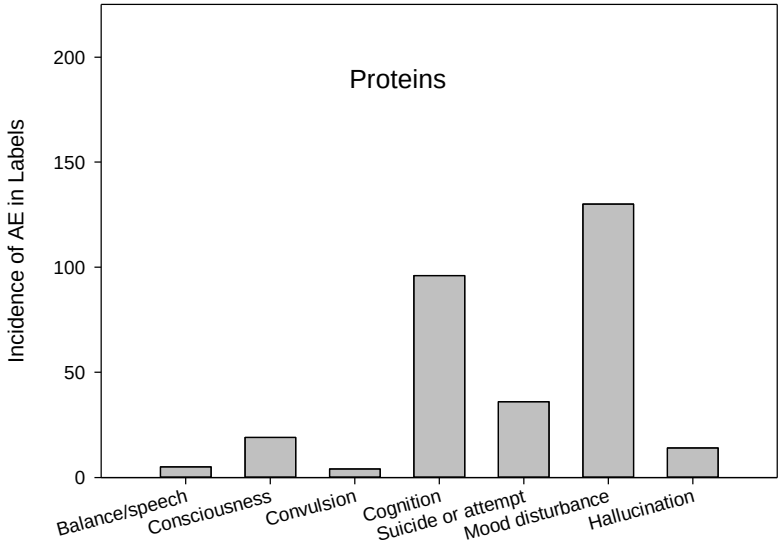
Only 1 instance of euphoric mood over 740 AEs

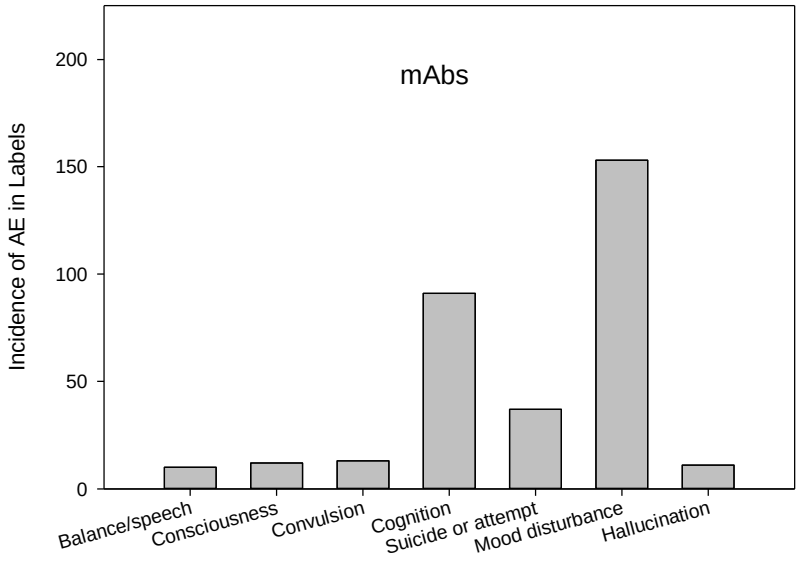
- No real signals for abuse potential

Breakdown of AE by biologic type



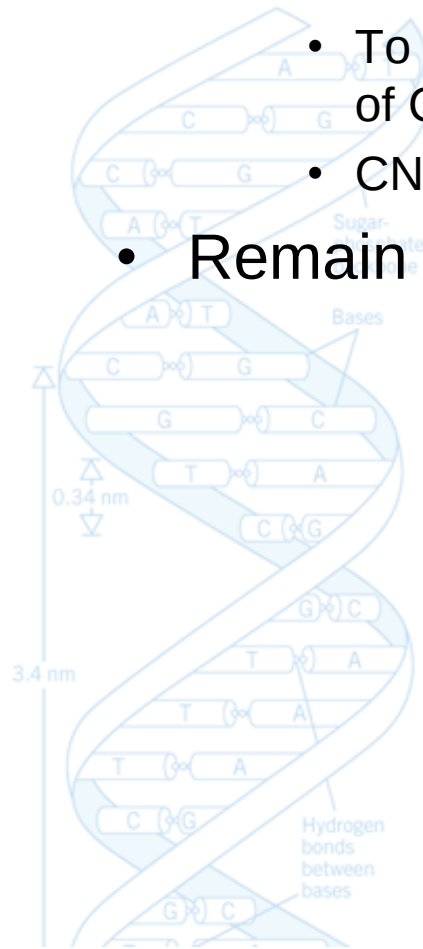
- Very similar frequency and pattern of AEs for mAbs and proteins
- Lower frequency, different pattern for vaccines
  - Healthy patients

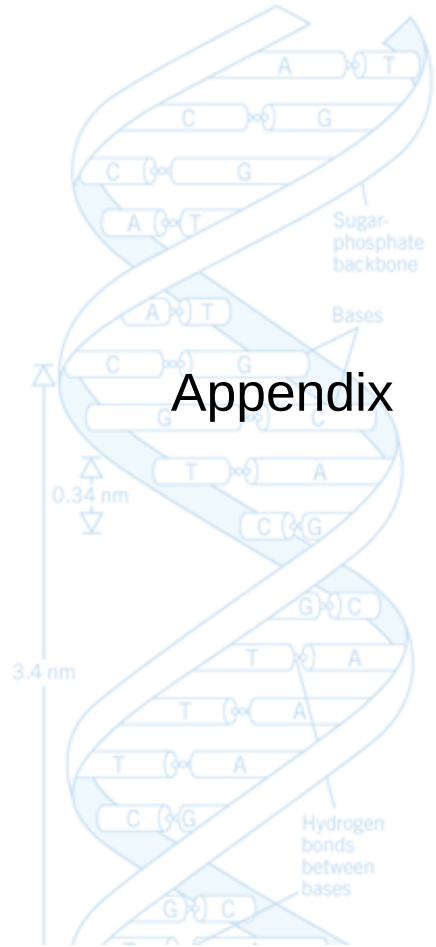




Summary

- Possible CNS-mediated effects of some biologics, especially in disease states
  - However, not equivalent to abuse potential
    - To date no abuse-related signals, but perhaps increased awareness of CNS safety should occur
    - CNS-related signals not detected in preclinical species
- Remain vigilant, especially in clinical populations

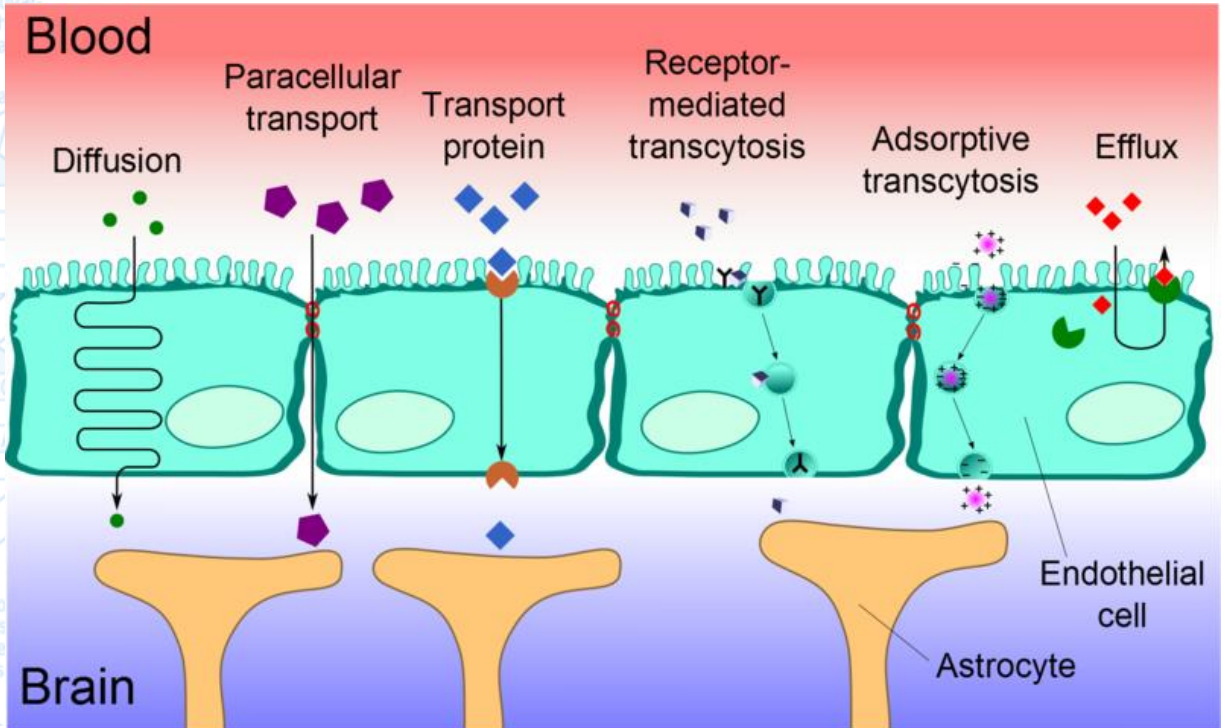



A
T
C
G
C
G
A
T
Sugar-
phosphate
backbone
A
T
Bases
C
G
G
C
T
A
0.34 nm
C
G
G
C
T
A
3.4 nm
T
A
T
A
C
G
Hydrogen
bonds
between
bases
G
C

Appendix

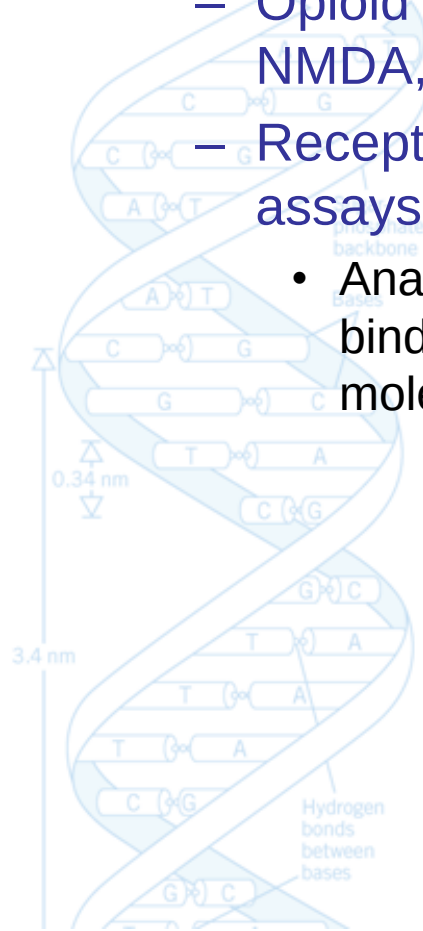
Considerations for Abuse Liability testing
Determining cause for concern – Brain penetration

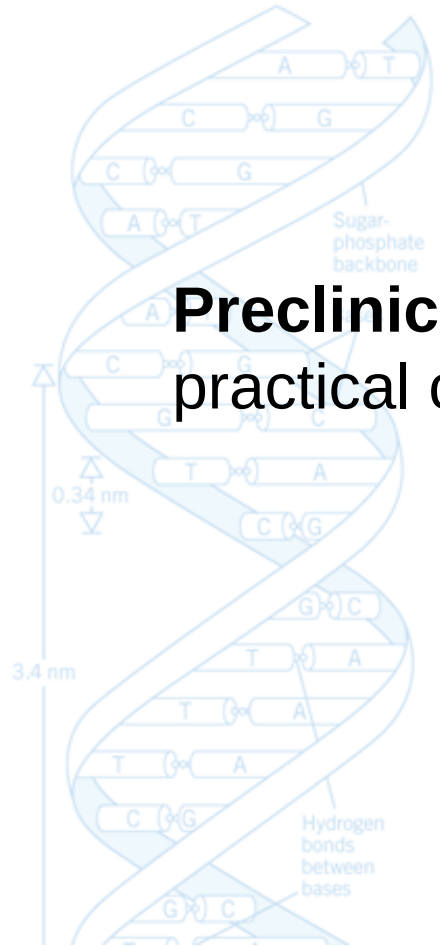
- Is a candidate molecule CNS active?
  - The blood brain barrier (BBB) is a serious challenge to drug delivery
    - Brain endothelial cells form tight junctions, have fewer fenestrations than endothelial cells in other organs, and possess high levels of efflux pumps (eg. P-glycoprotein)



Considerations for Abuse Liability testing
Determining cause for concern – Target specificity

- Guidance documents recommend *in vitro* screening to determine pharmacological site of action of a drug and binding to known targets involved in drug dependence
  - Opioid receptors, 5-HT and DA transporters and receptors, NMDA, GABA, nicotinic acetylcholine and cannabinoid receptors
  - Receptor binding assays are typically followed by functional assays to determine agonist vs. antagonist pharmacology
    - Analogous to the hERG assay (Vargas et al., 2008), CNS receptor binding/functional assays are unlikely to be appropriate for large molecules





Preclinical abuse liability assays – details and practical considerations related to molecule class

Common *in vivo* abuse liability assays
What are they meant to assess?

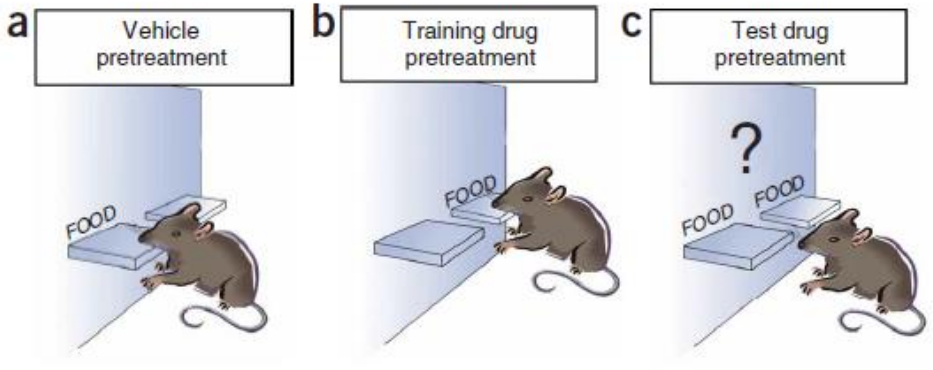
- Drug discrimination – can an animal distinguish between drug and vehicle, and does the drug seem similar to a known drug of abuse?
- Drug self-administration – will animals actively work to receive doses of drug?
  - If so, it is likely that the drug will be rewarding in humans
- Conditioned place preference – will an animal choose to spend time in an environment where it previously received the drug?
  - Again, if so it is likely that the drug will be rewarding in humans
- Dependence potential – does administration of the drug produce tolerance, and/or does discontinuation of the drug cause symptoms of withdrawal?

In vivo abuse liability studies
Important molecule-specific considerations

- Choice of species
  - Most AL assessments are conducted in rodents (rats)
  - Large molecules often don't cross-react with lower-order species, so studies in non-human primates may be required
- Pharmacokinetics/metabolism
  - SM drugs may be metabolized to active substances with binding profiles distinct from the parent compound; must assess
  - LM drugs characterized by long $T_{1/2}$ (i.e. on the order of 2 weeks)
    - In contrast to SM drugs, they wouldn't be expected to produce subjective effects that are short-lived
- Route of administration
  - Most SM drugs are formulated for oral administration
    - May not be amenable to re-formulation (IV, IP, SC), complicating drug discrimination and self-administration studies

Preclinical abuse liability assessment – *in vivo* techniques

- Drug discrimination
  - Animals are trained to respond on one lever after vehicle administration and on the other lever after drug administration

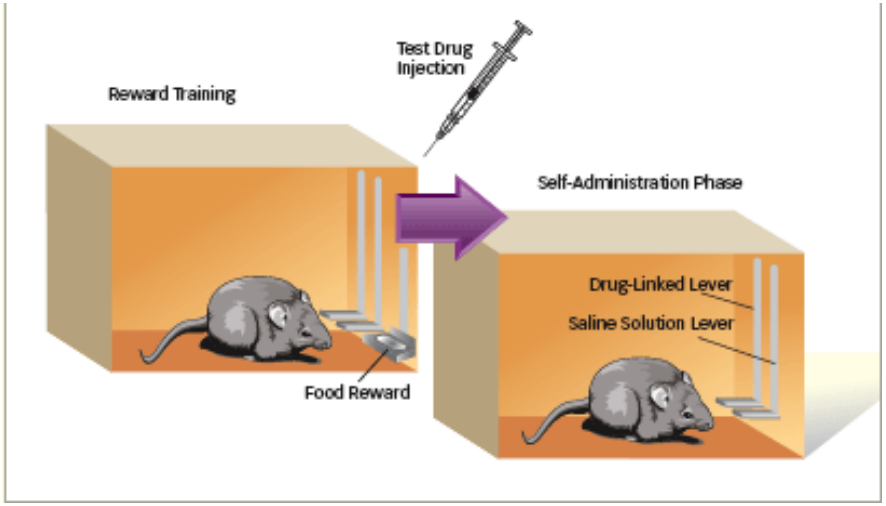


  - Once reliable responding has been established, the test drug is substituted
    - The animal chooses a lever, effectively describing whether the effects of the test drug resemble vehicle or the training drug
  - This technique can provide information on the CNS effects of a novel compound (i.e. what neurotransmitter system is affected)
  - Generalization to a drug known to cause dependence is not necessarily indicative of dependence potential (EMA)

Image credit: Solinas et al., 2006

Preclinical abuse liability assessment – *in vivo* techniques

- Drug self-administration
  - Animals are trained to respond on a lever for administration of drug, most typically via an indwelling intravenous catheter



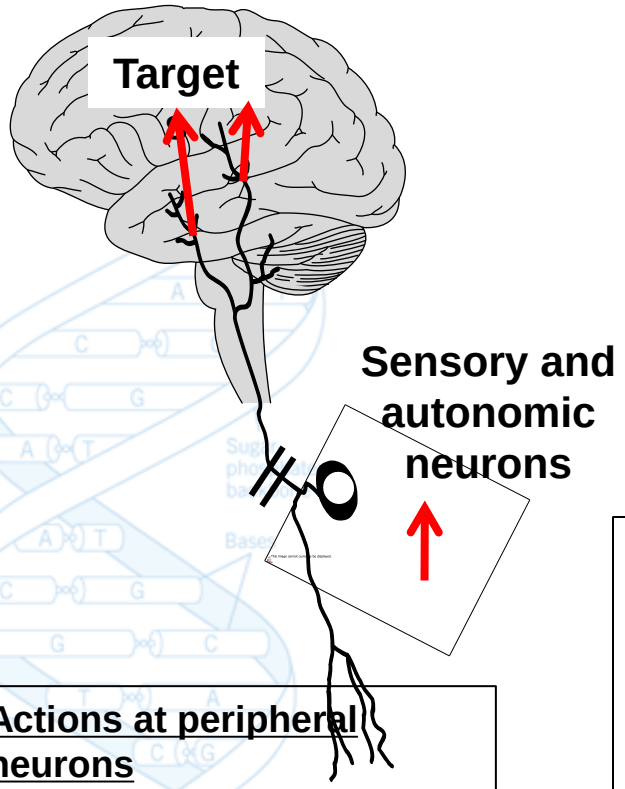
  - The use of different schedules of reinforcement can provide valuable information about the reinforcing nature of the drug (i.e. how hard will an animal work to receive a dose)

Image credit: Young-Wilson, 2006

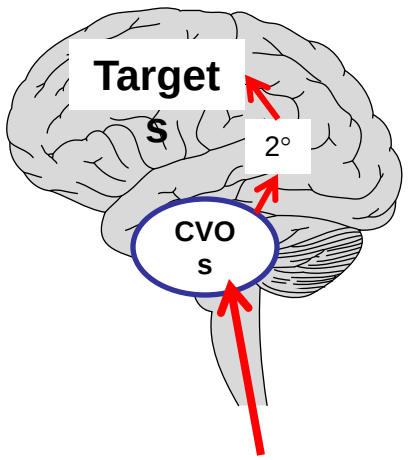
Preclinical abuse liability assessment – *in vivo* techniques

- Dependence assessment
  - Withdrawal effects are not necessarily correlated with abuse liability, but many abused drugs induce marked withdrawal symptoms that contribute to continued drug-taking
  - The drug candidate should be dosed for >1 month, ideally via the intended clinical route; doses should be supra-therapeutic
    - Possibility of including withdrawal assessments in sub-chronic/ chronic general toxicology studies
  - Drug administration is abruptly discontinued, and behavioral and physiological signs assessed
    - Behavior (clinical signs and locomotor activity), body temperature, blood pressure and heart rate
    - Consider the use of telemetry for physiological monitoring
  - Withdrawal is a concern primarily for short-acting drugs (i.e. SM); exposure tails gradually for drugs with a long half-life, mitigating withdrawal effects

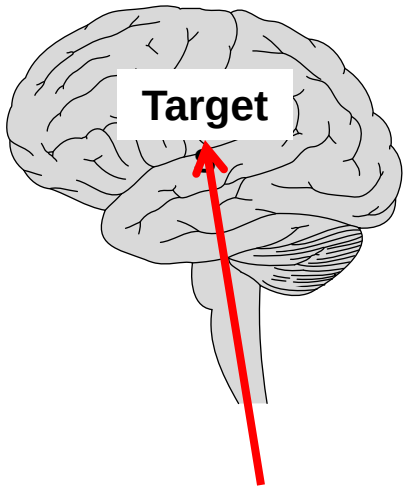
How Might Biologics Produce Neurological Effects? Slide Credit: Keri Cannon-Pfizer



Actions at peripheral neurons
- Activation of peripheral terminals of sensory and autonomic (i.e. vagus) nerves
- Signal transmitted to higher order centers in brain



Indirect actions in CVOs
- Passage into CVOs* and choroid plexus
- Activation of non-neural cells and release of 2nd messengers
- 2nd messengers pass into brain



Direct actions in the brain
- Penetration through BBB to respective targets in brain

These mechanisms are not mutally-exclusive and a biotherapeutic may employ all of these methods

*CVO: circumventricular organ

Saturable Transport Into Brain (Receptor/Carrier-Mediated) Keri Cannon-Pfizer

- Cytokines
  - IL-1α, IL-1β, IL-2, IL-6, IL-8, LIF
  - IFNα, IFNβ, IFNγ
  - CCL3 (MIP1)
  - TNFα
- Growth/trophic factors
  - NGF, BDNF, FGF, EGF, CNTF, GM-CSF
- Hormones/endocrine
  - Insulin
  - IGF-1, IGF-2
  - Ghrelin, leptin
  - GLP-1
- Lipoproteins
  - LDL, HDL, VLDL
- LRP1 mediated transport
  - Factor VIIa, factor VIIIa, factor Ixa, C1 inhibitor, complement C3, ApoE, MMP-9, MMP-13, PDGF, SAP
- Other mechanisms
  - Couple to transferrin receptors
  - Pegylation
  - Diphtheria toxin receptor (a.k.a. heparin-binding EGF precursor)

*Please note that this list is not exhaustive