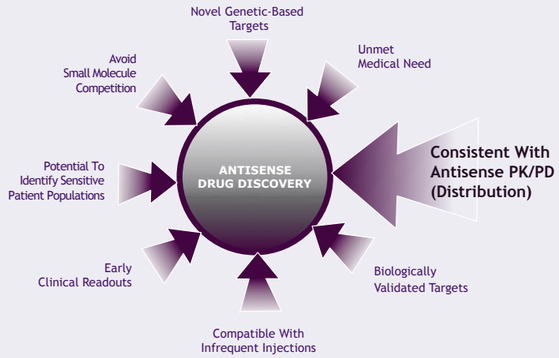
Pharmacokinetics (PK) & Pharmacodynamics (PD): Properties of Antisense Drugs

CONSISTENT & PREDICTABLE

Drug Discovery & Development Strategy: Consistent PK/PD is an Important Component



Extremely Well Understood & Predictable PK Properties

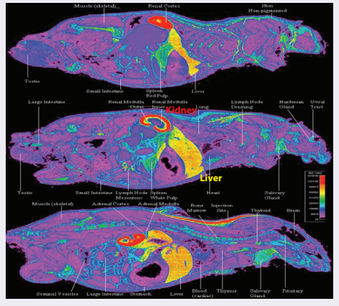
- **Absorption**
  - Delivered directly (IV) or well absorbed from injection sites (SC)
- **Distribution**
  - Highly plasma protein bound (≥90%)
    - Binding does not displace small molecules or vice versa. Low affinity, non-specific & hydrophilic interactions
    - Binding to plasma proteins prevents renal clearance & promotes uptake in tissues
  - Dose-dependent, rapid & near complete distribution from plasma to tissues. Trough plasma levels accumulate corresponding to tissue accumulation
    - degree of accumulation dependent on antisense drug half-life & frequency of administration
  - Highest tissue concentrations seen in kidney & liver
- **Metabolism**
  - Metabolism process is different from small molecules, thereby avoiding drug-drug interactions
  - Tissues cleared by nuclease metabolism to shorter nucleotides & oligo fragments
  - Tissue $T_{1/2}$ = 14 to 30 days; chemistry & sequence dependent
- **Elimination**
  - Urinary excretion of parent drug & nuclease products

Predictable Behavior Allows For Faster Drug Development & Increases Probability of Success

- **Consistent/Predictable**
  - PK properties across the class of second-generation antisense drugs vary little from one sequence to the next
- **Simple**
  - Known PK properties simplifies preclinical & clinical dose regimen selection, & allows faster progress through drug development
- **Convenient**
  - Weekly subcutaneous (SC) dosing allows more convenient administration to patients than intravenous (IV) dosing
- **Effective**
  - Pharmacology is potent, sequence-dependent, specific, long-lived & directly related to concentrations in target tissues/cells
- **Versitile**
  - PK/PD properties allow a wealth of targets in various tissues to be amenable to antisense technology

All Second-Generation Drugs Have Similar Tissue Distribution = Shared & Predictable Safety Profile

Rank Order: Kidney > Liver > Spleen/Lymph nodes > Bone marrow



48 Hours After S.C. Injection in a Male Rat

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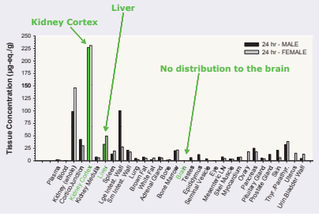


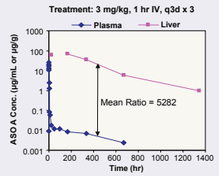
Consistent/Predictable

Consistent & predictable PK properties across the class of second-generation antisense drugs & between species (including humans)

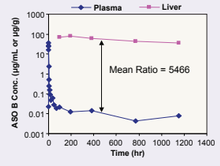
- **No guesswork when we test new antisense drugs in the clinic or in animals**
  - Unlike most other drugs in development, we already know the general PK properties of antisense drugs in humans & animals
- **Can leverage lessons & information learned from previous or current antisense drugs under development to apply to future developed antisense drugs**
  - PK properties consistent across sequence
  - PK properties similar in mice, rat, dog, monkey & human
- **Antisense drugs share similar physical/chemical properties & chemical structure**

Liver Antisense Drug Concentrations Are Predicted by Plasma

ASO A



ASO B



Tissue Elimination Predicted by Plasma

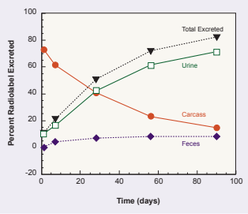
Sequence	Monkey Liver	$t_{1/2}$ (days) Kidney[b]	Human Plasma
ASO A	13	17	13
ASO B	7.7	16	16
Mipomersen	34	33	31

Concentrations represent parent drug & normalized to 3 mg/kg/week dose

[b] Kidney cortex

Yu et al. *DMD* 2007 35(3): 460-468

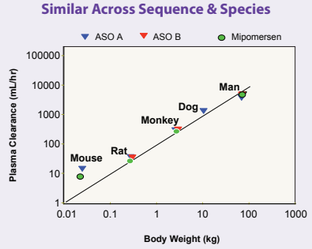
Antisense Drugs Eliminate in Urine



SIMPLE

- **Bioanalytical assay methods (for biological matrices such as plasma, tissues & urine) are similar for all antisense drugs: simplifying assay development & validation**
- **Known PK properties simplifies preclinical & clinical dose regimen selection, & allows faster progress through drug development**
  - One of the reasons for drug failures during development is suboptimal PK. While safety, efficacy & toxicology dominate reasons for failure, suboptimal PK can play a key role in all of these
  - Doses required to produce appropriate exposure in toxicology studies are known
  - Typical human dose range of antisense drugs is 50–400 mg (may be higher in oncology)
  - Long half-life (2–4 weeks) allows once weekly (or as little as once monthly) dosing of antisense drugs
- **Only simple saline solutions required to effectively deliver antisense drugs**
  - No need for liposomal formulations or lipophilic conjugates, as used for dsRNA

Pharmacokinetics is Similar Across Sequence & Species



Clinical Plasma PK Similar Across Antisense Drugs

PK Parameter	ASO A* 5-10-5	ASO B 5-10-5	Mipomersen 5-10-5	ASO C* 3-9-8	ASO D* 4-13-4
Infusion Duration (hr)	1	1	2	1	2
C_{max} (µg/mL)	26	22	22	14	23
AUC (µg-h/mL)	49	57	68	30	65
$t_{1/alpha}$ (hr)	1.5	1.8	1.3	1.4	2
$t_{1/elim}$ (days)	12	≤15	31	≤24	nm
CL (L/hr)	2.9	2.4	2.1	4.8	2.4

(200 mg IV Infusion Dose)

*2 mg/kg (approx. 160 mg)

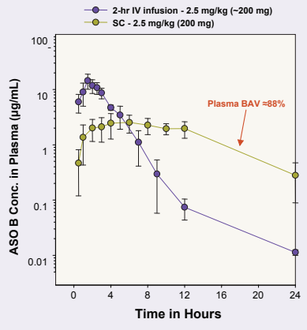
Yu et al. *DMD* 2007 35(3): 460-468

CONVENIENT

Can be Given Conveniently by Multiple Routes of Administration

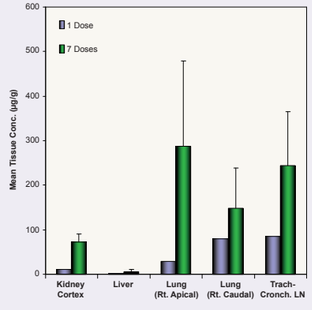
- **Subcutaneous (SC) dosing allows more convenient administration to patients than intravenous (IV) dosing**
- **Possibility of oral administration in the future with more potent antisense drugs (next-generation chemistries)**
- **Other routes of administration include pulmonary (inhalation), rectal (enema), topical, ocular (intravitreal), intrathecal, intracerebroventricular & intradermal**

Multiple Routes of Administration *Convenient Subcutaneous Self-Administration Distribution is Similar to IV*



Multiple Routes of Administration *Direct Administration to Lung: Improves Distribution to Lung*

5 mg/kg dosing via aerosol inhalation in monkeys



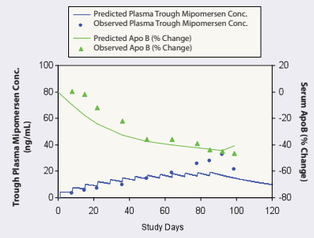
Error bars represent Standard Deviation

Yu et al, AAPS NBC, San Diego (2007)

EFFECTIVE

- **Pharmacology is:**
  - Potent with second-generation antisense drugs
    - ED_{50} of ~15-25 mg/kg/wk in mouse & ~200 mg/wk (~3 mg/kg/wk) in man
    - Enhanced potency with next-generation chemistries
    - Changes to gap design, optimization of length or chemical modifications may further enhance potency & PK
  - Sequence-dependent & specific (mechanism of antisense action predicts that increasing sequence mismatches reduces activity)
  - Directly related to concentrations in target tissues (cells) with respect to both activity & duration
- **Concentrations in target tissues in humans predictable from dosing in monkeys**
- **Effective tissue concentrations generally consistent from one target to the next**
- **Plasma concentrations seen after the drug has distributed from the blood stream & equilibrated with tissue antisense drug levels provides a direct surrogate of tissue concentrations (PK/PD relationships can be established & modeled)**
- **Onset of action is not immediate, but duration is consistent with elimination half-life from tissues or target cells**

Effective Doses for Antisense Drugs are Predictable & Known



Geary et al, *Antisense Drug Technology 2nd Ed.*, Ch. 11 (2008)

VERSATILE

- **Given the established PK & PD properties of antisense drugs, there are a wealth of targets amenable to antisense technology**
  - Primary organs of distribution known (select targets in therapeutic areas consistent with antisense PK/PD)
  - Stable drugs with long half-lives (choose diseases compatible with infrequent injections; deliver drugs by essentially any route of administration)
- **In various tissues in which antisense drugs distribute, scores of targets documented & published**
  - Can create drugs to novel genetic-based targets
  - Ability to treat "undruggable" targets (avoid small molecule competition; potential to identify sensitive patient populations)
  - Ability to treat unmet medical needs

SUMMARY

Antisense Technology Enables Efficient Drug Development & Increases Probability of Success

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  - PK properties across the class of second-generation antisense drugs & between species (including humans) vary little from one sequence to the next
- **Simple**
  - Known PK properties simplify preclinical & clinical dose regimen selection & allows faster progress through drug development
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- **Effective**
  - Pharmacology is potent, sequence-dependent, specific, long-lived & directly related to concentrations in target tissues/cells
- **Versatile**
  - PK/PD properties allow a wealth of targets in various tissues to be amenable to antisense technology (broad therapeutic applications for many different diseases & conditions)