Time matters! – Why PK/PD is important for oligo development

Oligonucleotide Therapeutics Society Webinar
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Why do We Need to Know This?

ADME

Absorption, Distribution, Metabolism and Excretion

DMPK

Drug Metabolism and Pharmacokinetics

Safety

Safe and Tolerable use with sufficient margins to effective exposure

In order to understand :

- *when to dose*
- *how much to dose*
- *who should receive the dose*

What is Pharmacokinetics?

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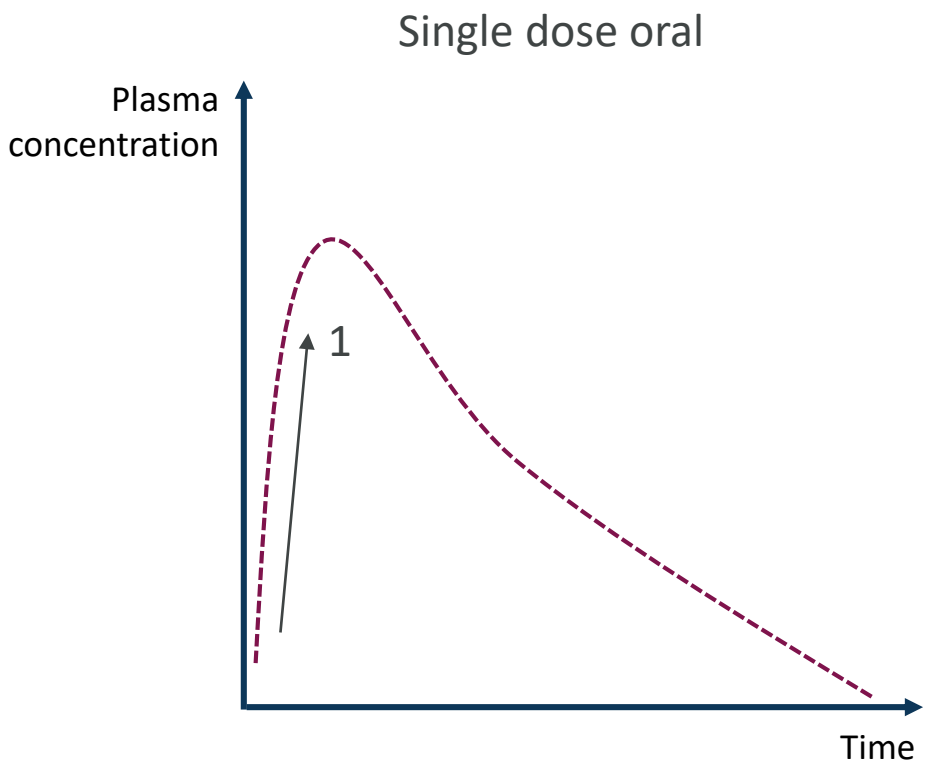
It is the study of what the body does to the drug

General Pharmacokinetics of a Drug Molecule:

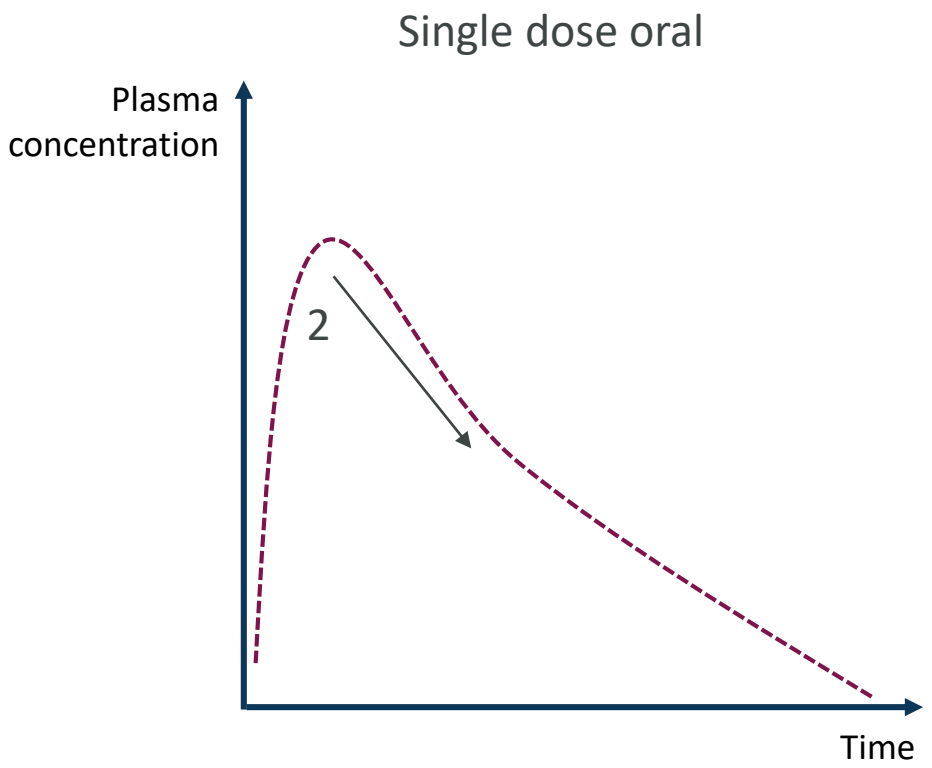
1. The drug administered orally – rendering an increase in plasma concentration



General Pharmacokinetics of a Drug Molecule:

1. The drug administered orally – rendering an increase in plasma concentration

2. Secondly the absorption process is cancelled out by distribution (and elimination)



General Pharmacokinetics of a Drug Molecule:

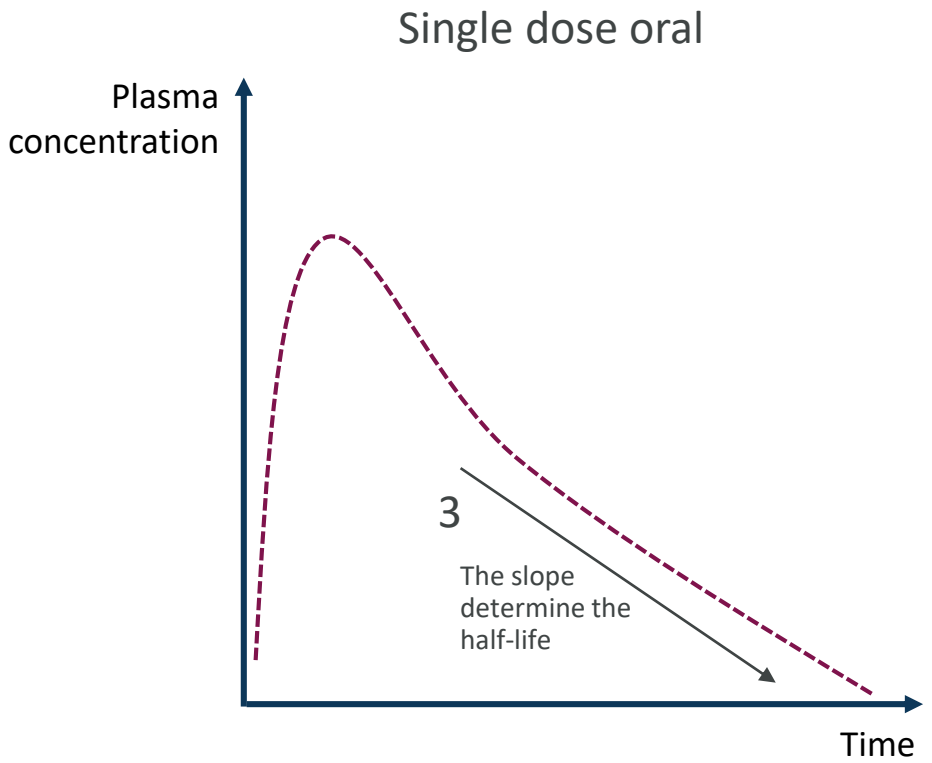
1. The drug administered orally – rendering an increase in plasma concentration

2. Secondly the absorption process is cancelled out by distribution (and elimination)

3. Thirdly, the elimination of the drug is the process regulating the exposure in the plasma

Unless a new dose is given, the concentration will continue to zero

The fraction of the dose reaching systemic circulation, after the liver is called *bioavailability*



The Concept of Half-life:

The half-life is defined as the time to half the drug concentration level

- The parameter can be of value for assessing duration of pharmacological action – through exposure
- Drug elimination is a first-order process – constant proportion of drug is lost per time unit
- Since there is a rapid distribution phase (time <28 days) followed by a longer elimination phase (time >28 days) we separate *initial* versus *terminal* half-life
- The half-life $(t_{1/2})$ is dependent on the elimination rate (k) which is related to the ratio between volume of distribution (V) and clearance (CL) :

$$t_{1/2} = \frac{Ln(2)}{k} = \frac{Ln(2) \times V}{CL}$$

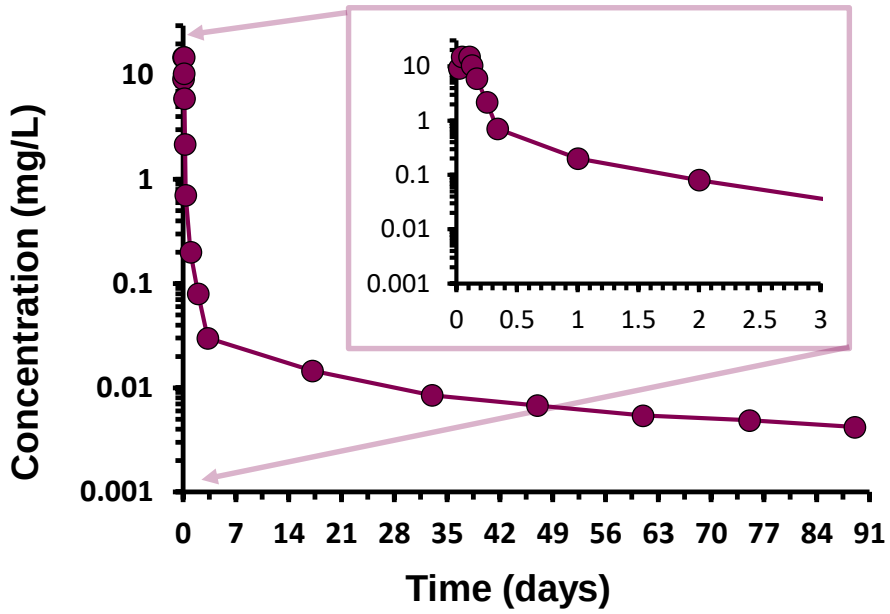
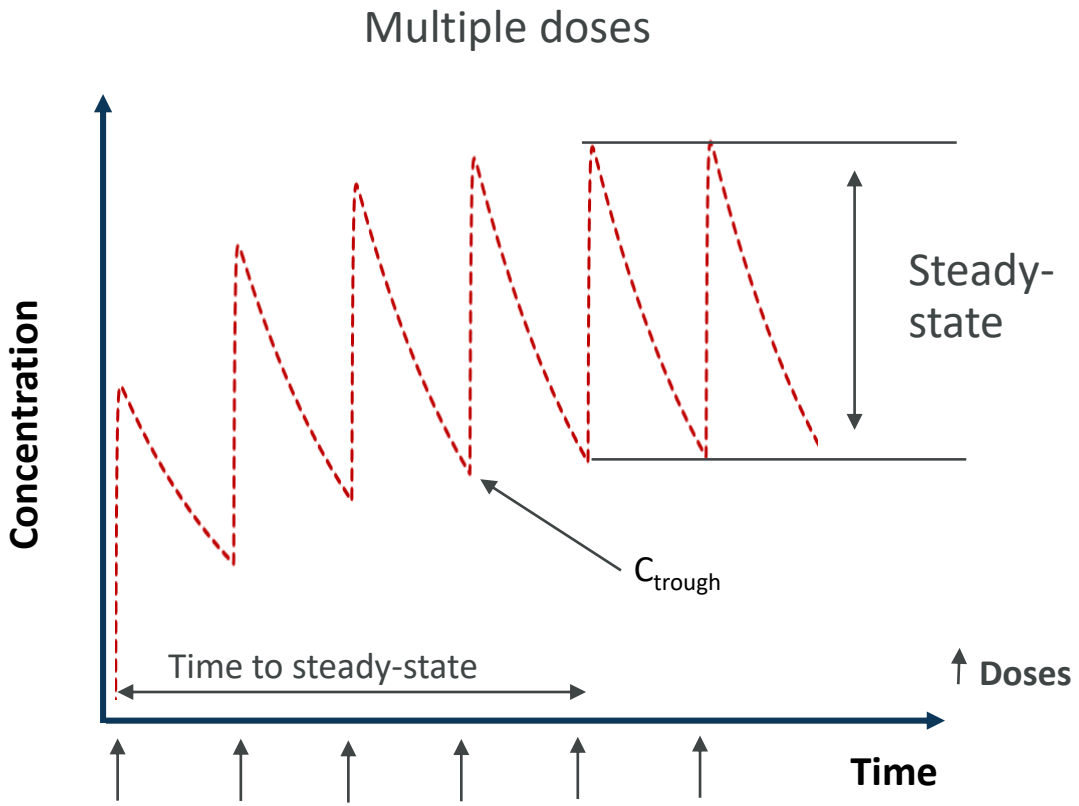


Figure adapted from Olof Gissberg et al. (eds.), Oligonucleotide-Based Therapies: Methods and Protocols, Methods in Molecular Biology, vol. 2036,Springer Nature 2019

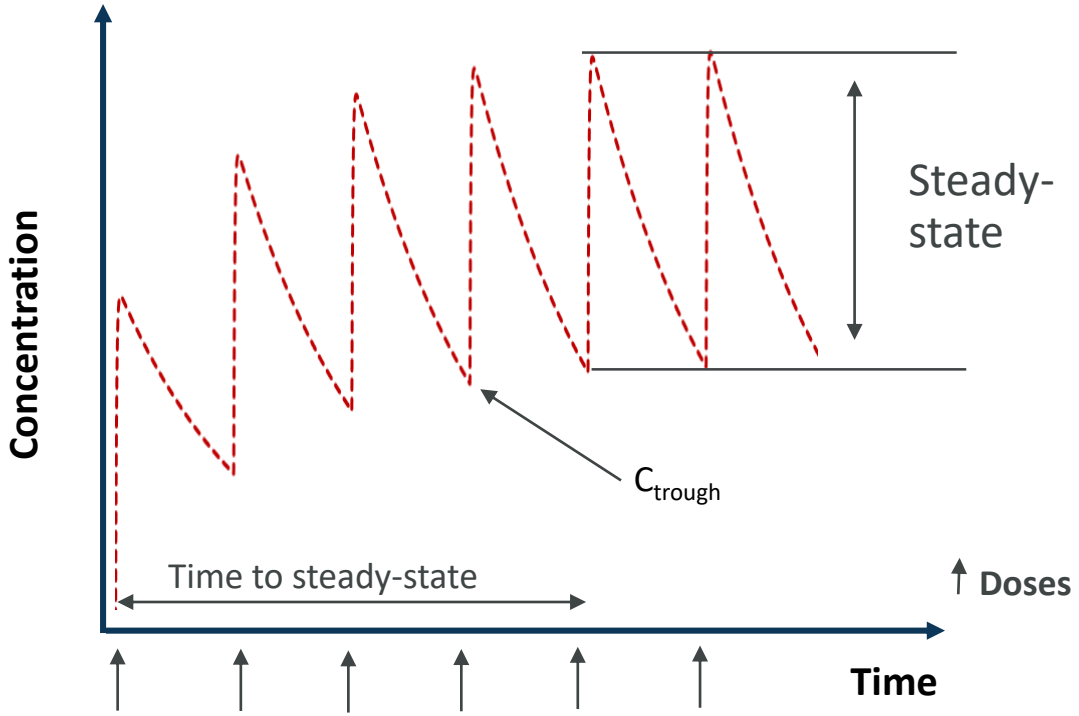
The Impact of Half-life on Drug Exposure and Accumulation:



- For repeated dosing there is *always* 3-5x half-life to reach steady-state
- No more incremental increase in exposure with the same dose and dosing interval

The Impact of Half-life on Drug Exposure and Accumulation:

Multiple doses



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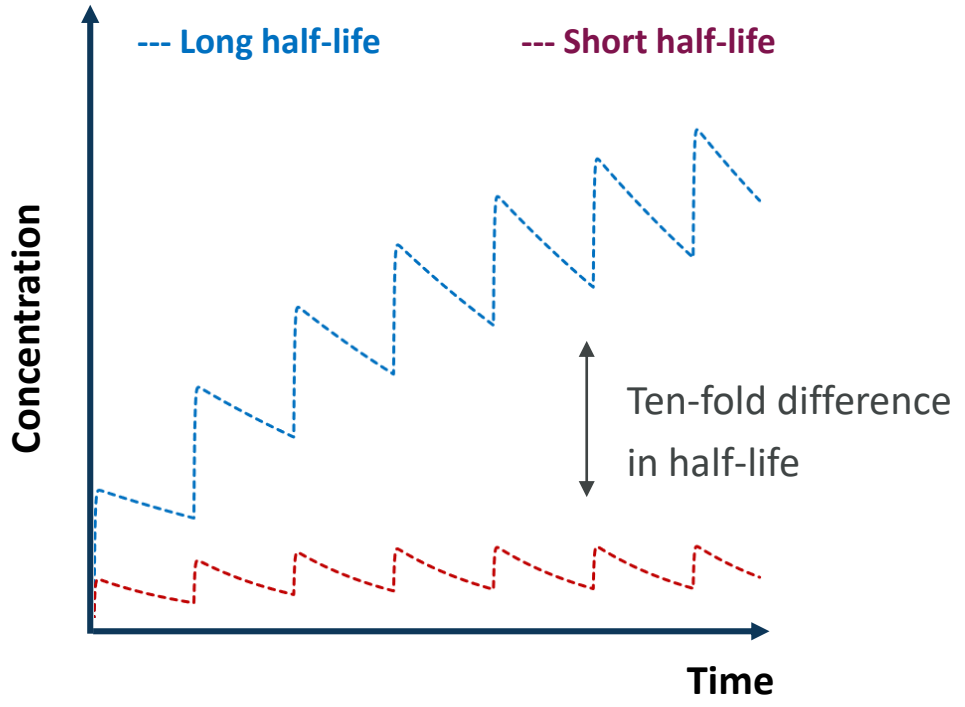
Comparing long vs short half-life



- A long half-life may enable a less frequent and lower doses as accumulation is pronounced
- Different ON sequences, target and target organs may have <u>different</u> half-life

We can Use the Accumulation Index to Estimate Half-life

If we cannot take frequent PK samples to estimate the half-life (from the curve slope) the degree of accumulation can be used as a surrogate through:

$$a = \frac{1}{1 - e^{-\left(\frac{\log(2)}{t_{1/2}}\right) \times \tau}}$$

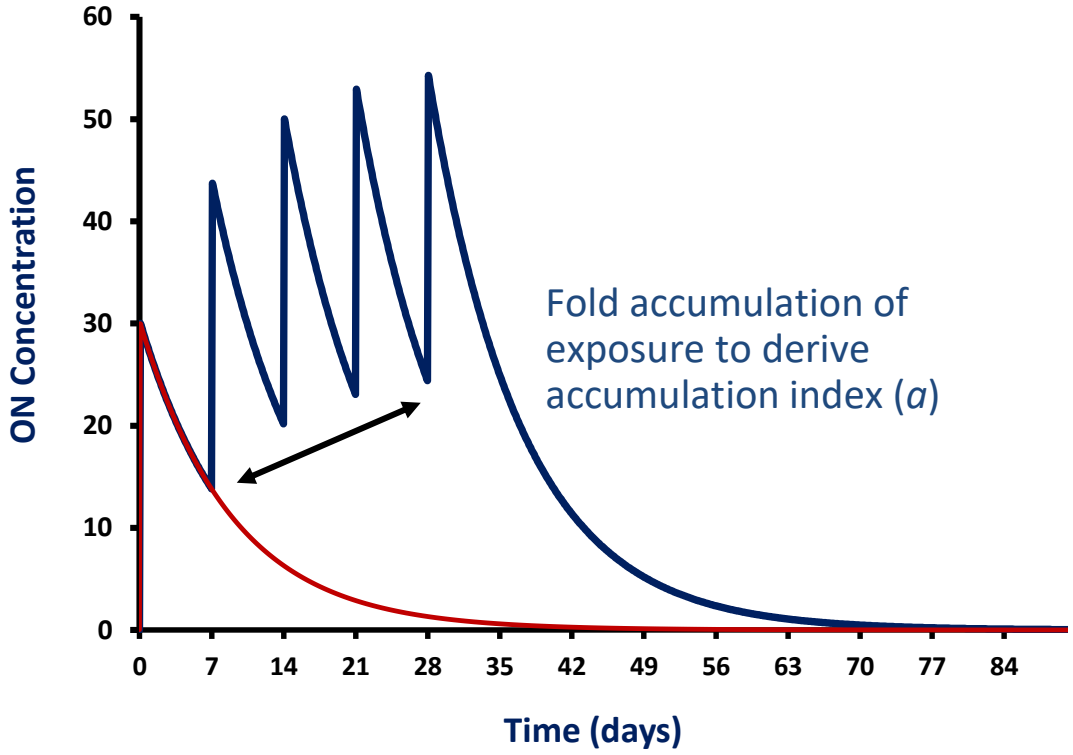
re-arrange

$$t_{1/2} = -\frac{\log(2) \times \tau}{log\left(\frac{a-1}{a}\right)}$$

a = ackumulation index

τ = Dosing interval (e.g. 7 days as in figure to the right)

ON exposure from single vs multiple doses

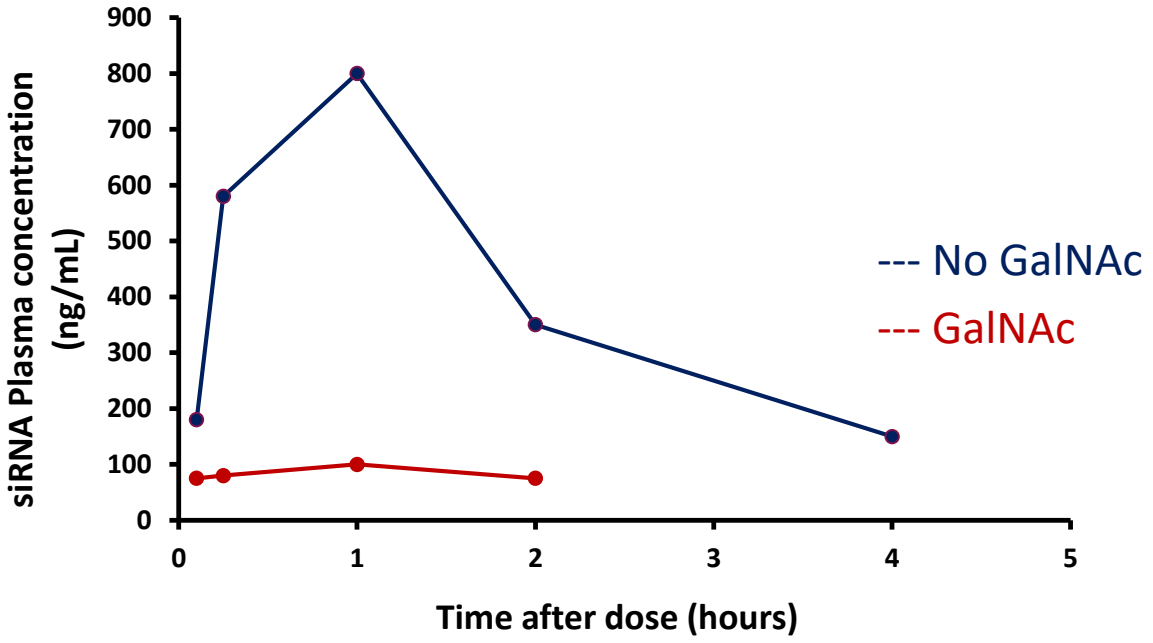


If C_{trough} is doubled from day 7 to day 28, then a=2

Figure and equations adapted from Olof Gissberg et al. (eds.), Oligonucleotide-Based Therapies: Methods and Protocols, Methods in Molecular Biology, vol. 2036,Springer Nature 2019

Plasma Exposure is Dependent on Conjugation

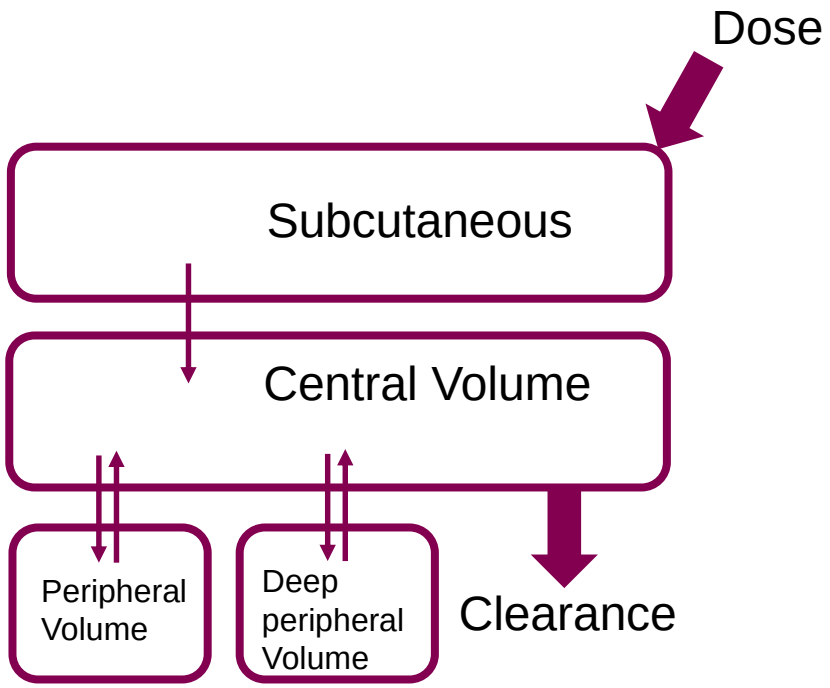
- The ON exposure at the target is more relevant than the concentrations in plasma
- The disposition of the ON is sequence and target dependent
- Saturation of liver uptake leads to higher plasma exposure
- The effect (mRNA knockdown) can be used as a surrogate for exposure in the target tissue
- Distinguish between productive and non-productive uptake in cells and tissue
- Quantitating the ON exposure across tissues may be of interest for both safety and efficacy read-outs

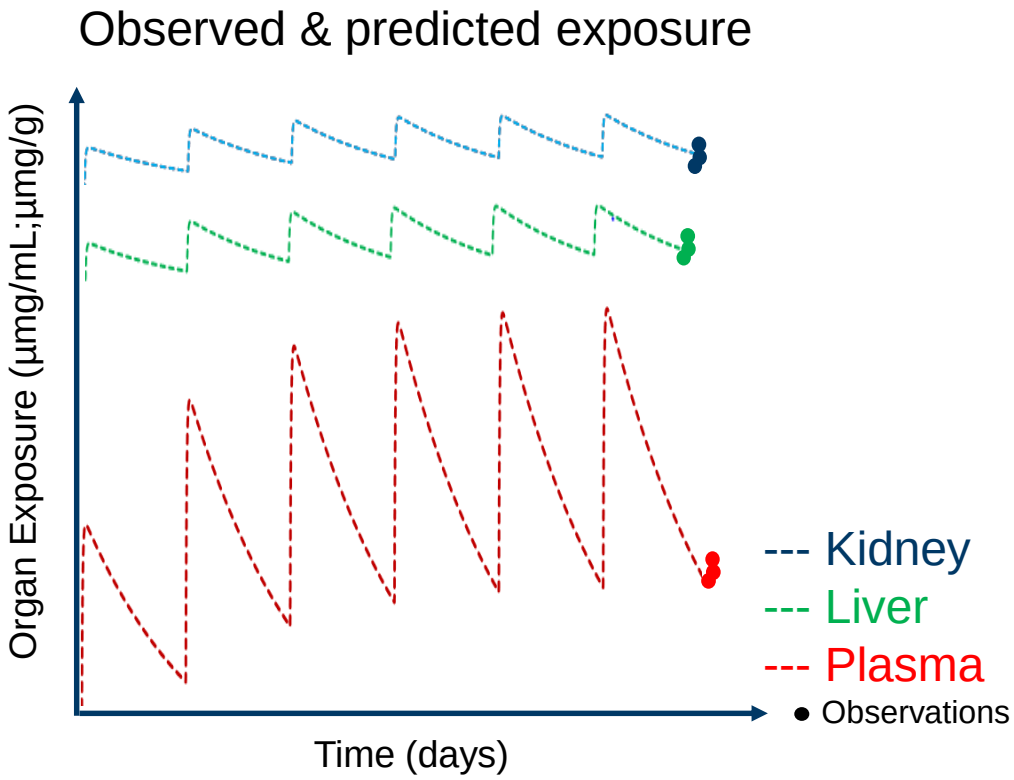


- The ON is more effectively “cleared” from plasma when it is conjugated to GalNAc
- Shifted exposure ratio liver/kidney

Figure adapted from: Kippendorf and Bon, Preclinical and clinical PK of GalNAc SSOs at doses below and above ASGPR saturation, DIA meeting, North Bethesda MD, USA Oct 28-30 201

The Model can also be Used to Predict ON Exposure in Tissue





The model can also be used for predictions of ON exposure in different tissues

General Pharmacokinetic Parameters and Definitions:

CL - is the clearance of the drug and a measure of the elimination of the drug

V - is the volume of distribution of the drug and a measure of the drug tissue distribution

$T_{1/2}$ - the half-life of the drug

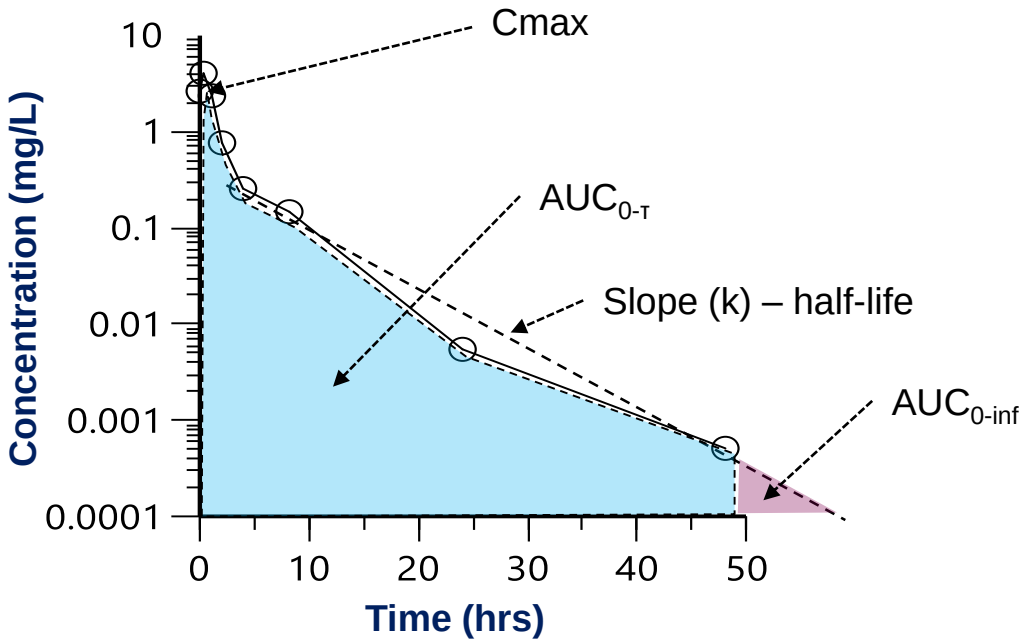
C_{max} - is the maximum observed concentration and represent the maximum exposure level

T_{max} - is time to C_{max} and is sometimes given with the C_{max}

C_{trough} - is the trough concentration provides information of the lowest exposure level, taken right before dosing, in a repeated dosing study

AUC - is the area under the curve and represent the total drug plasma exposure level over time

$$AUC = \frac{Bioavailability \times Dose}{CL}$$



The extrapolated curve ($AUC_{0\text{-}inf.}$), should not exceed about 20% of the $AUC_{0\text{-}\tau}$.

IV/SC dosing T_{max} at or close to 0 h

Ref. and figure adapted from Olof Gissberg et al. (eds.), Oligonucleotide-Based Therapies: Methods and Protocols, Methods in Molecular Biology, vol. 2036,Springer Nature 2019

What is Pharmacodynamics?

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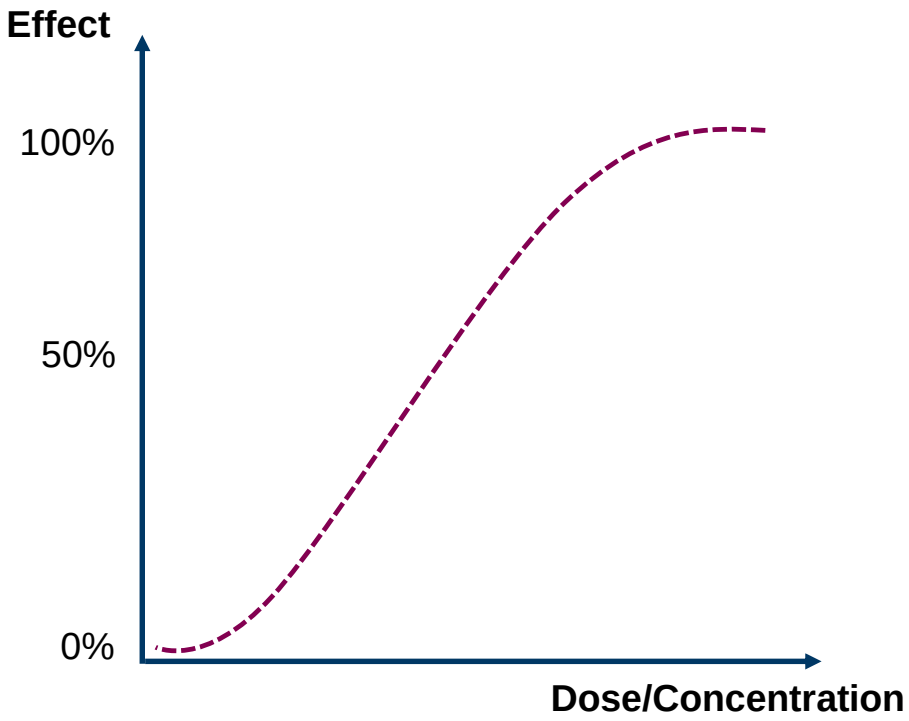
It is the study of what the drug does to the body

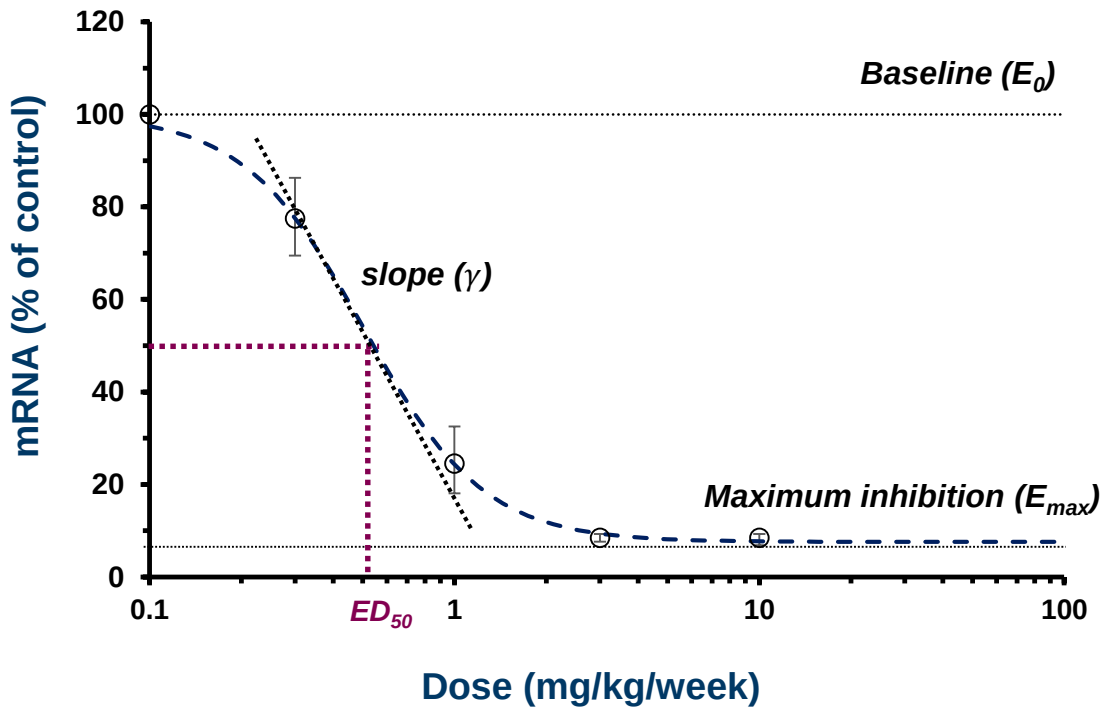
Relating Drug Levels to the Pharmacological Effect



- Commonly characterized by the exposure-response relationship with an E_{max}-function
- A direct effect model, i.e. no time delay between exposure and effect
- The time component can be very important especially when assessing the dose-response relationship
- Continuous biomarkers and their relationship to the levels of drug available
- PK half-life and effect half-life are NOT the same thing

$$E = \frac{E_{max} \times Dose}{ED_{50} + Dose} \qquad E = \frac{E_{max} \times Concentration}{EC_{50} + Concentration}$$

Expansion of the Exposure-Response Relationship



E_0 is the baseline effect given by either vehicle or control (scrambled) ON

E_{max} is the maximum inhibitory (or stimulatory) effect observed; may be warranted to assume the max effect is 1 (i.e. 100% inhibition is achievable)

ED_{50} is the dose that renders 50% of the maximum effect

Slope is the slope of the relationship
low value – flat relationship
high value – steep relationship (on/off)

$$E = E_0 - \frac{E_{max} \times Dose^{\gamma}}{ED_{50}^{\gamma} + Dose^{\gamma}}$$

"Absolute inhibition"

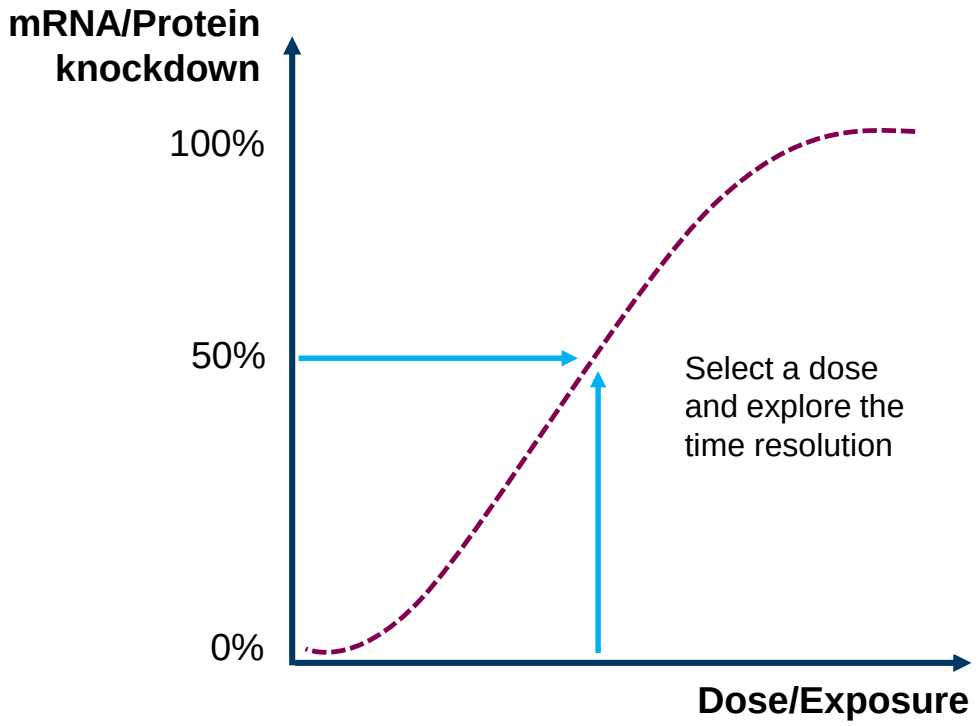
$$E = E_0 \left(1 - \frac{E_{max} \times Dose^{\gamma}}{ED_{50}^{\gamma} + Dose^{\gamma}}\right)$$

"Relative inhibition"

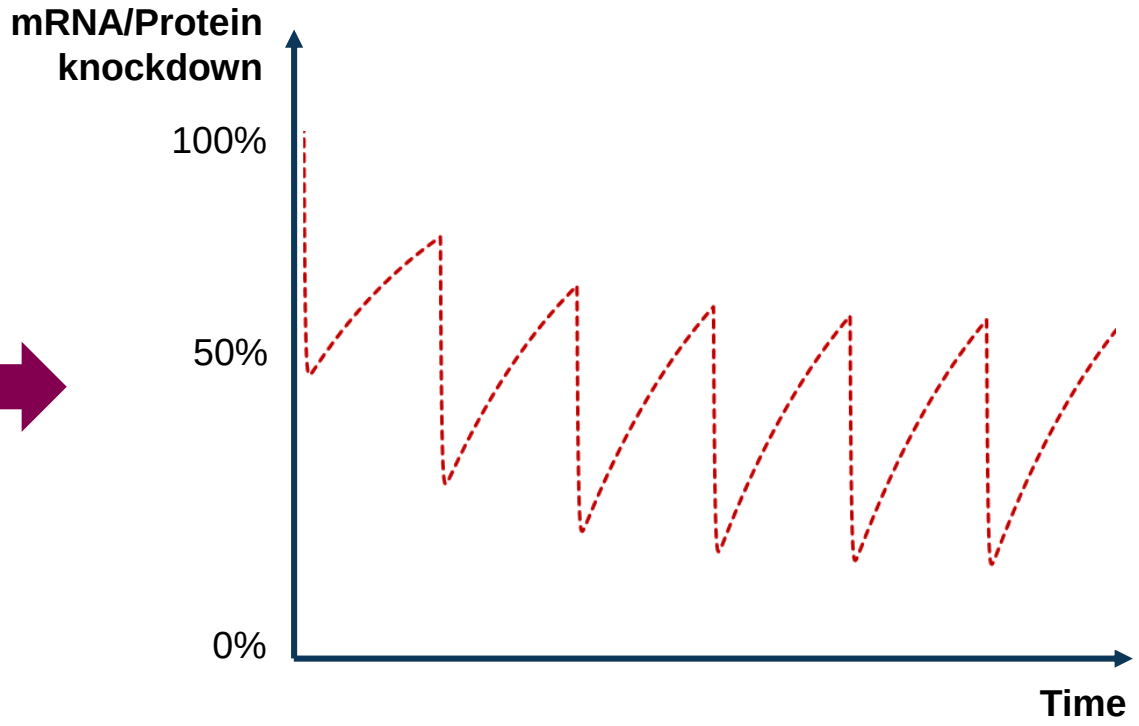
Figure and equations adapted from Olof Gissberg et al. (eds.), Oligonucleotide-Based Therapies: Methods and Protocols, Methods in Molecular Biology, vol. 2036,Springer Nature 2019

Time is an Important Component also for Effect

"Snapshot in time"



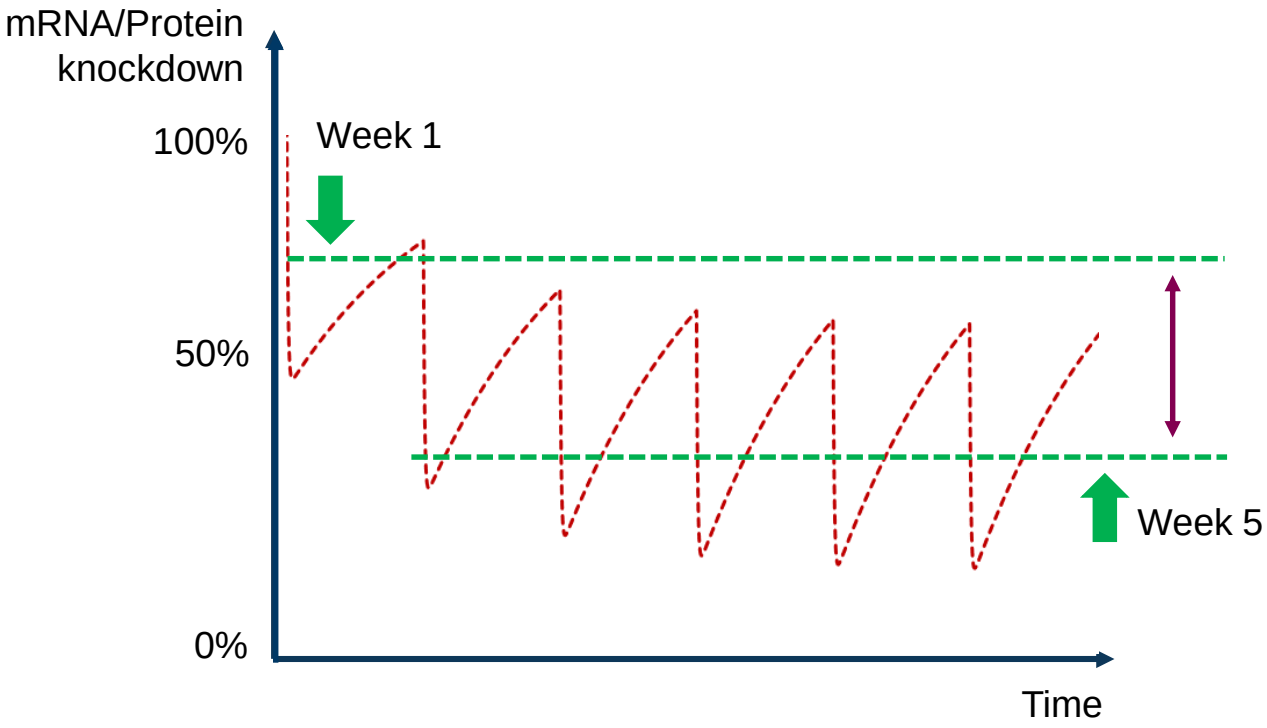
Multiple doses – accumulation of effect



Accumulation of effect over time, depending on either: drug exposure acc. or **the effect half-life**

Pharmacodynamics – "What the Drug Does to the Body"

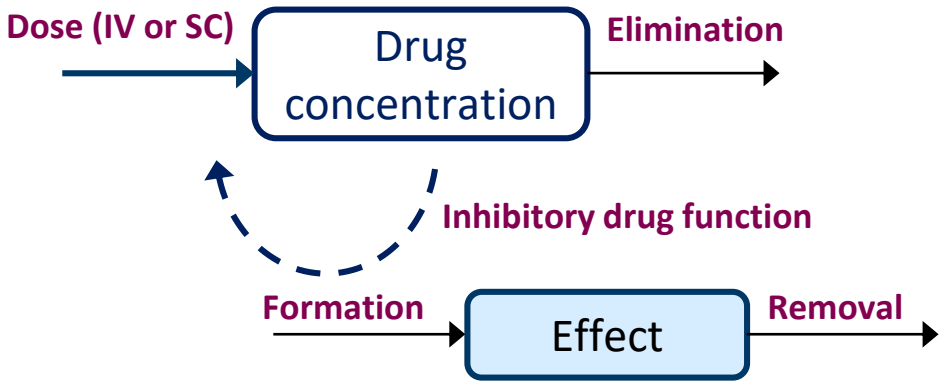
Multiple doses – accumulation of effect



PD $t_{1/2}$ time to reach 50% of the maximum effect

Onset/offset how fast the effect initially comes and for how long the duration is

To link exposure and effect over time we can use an indirect response model:



where both the time course of the ON and the effect are taken into account

Model figure adapted from Olof Gissberg et al. (eds.), Oligonucleotide-Based Therapies: Methods and Protocols, Methods in Molecular Biology, vol. 2036,Springer Nature 2019

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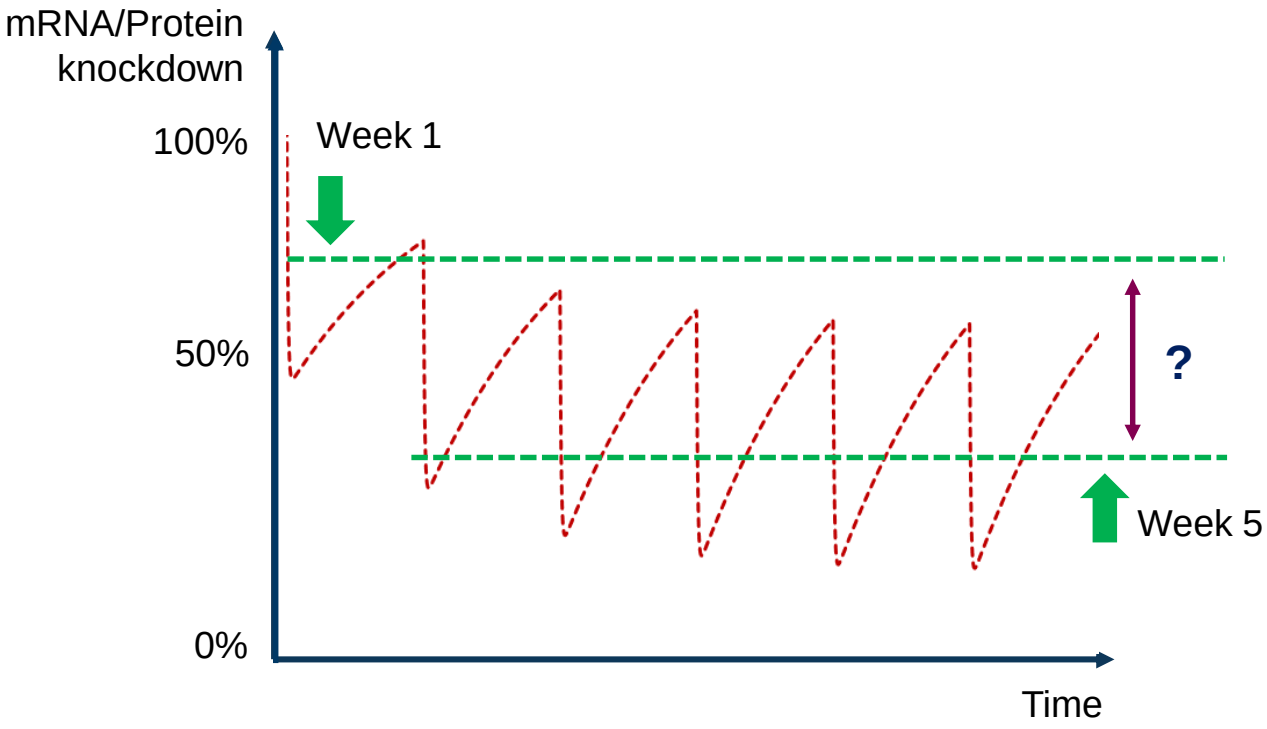

Impact of making your dose-response assessment at week 1 compared to week 5?

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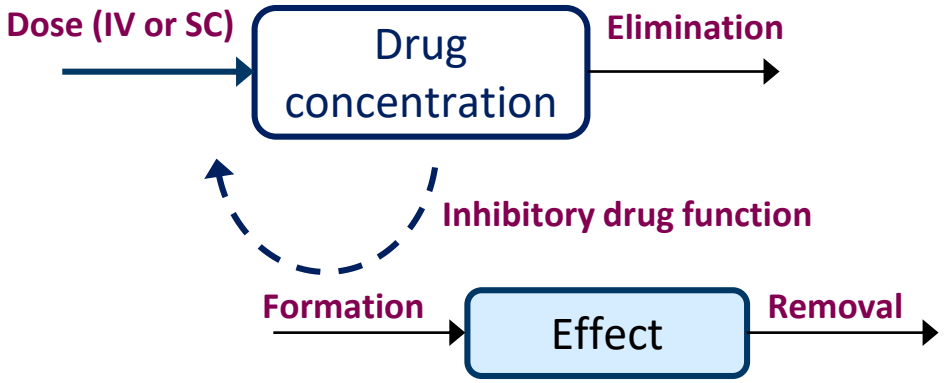

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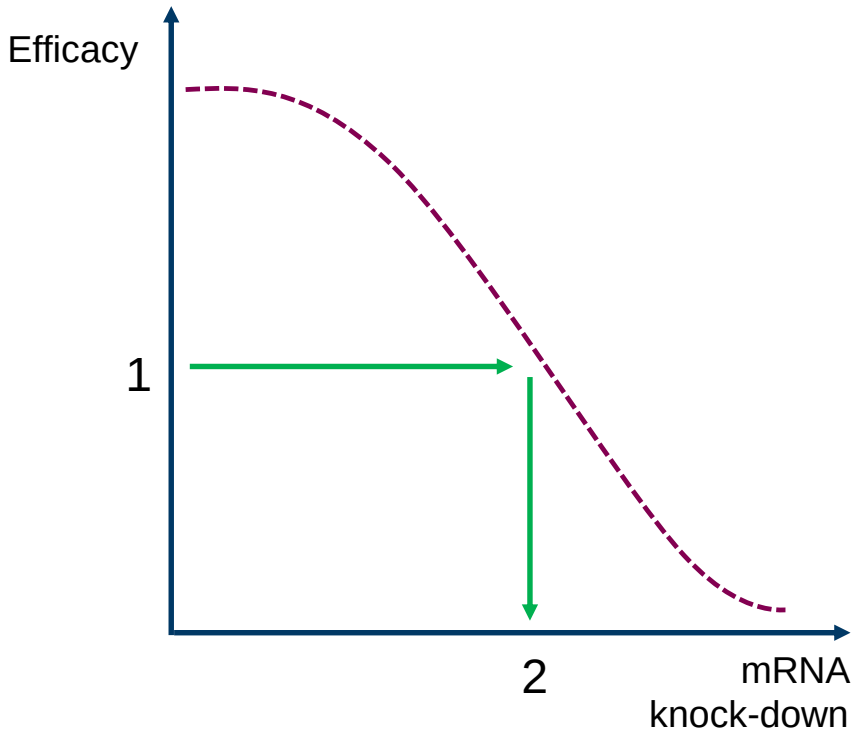
Establishing the Link Between Knockdown and Efficacy

We want to establish the quantitative relationship between the level of knock-down to a <u>disease modifying effect</u>



- A relevant disease model for your disease – *e.g.* diet induced non-alcoholic steatohepatitis (NASH) mouse model
- Difference between establishing proof-of-concept (only one dose needed) and establishing the quantitative link
- Select doses that are expected to have a wide distribution in knock-down in order to cover the knock-down curve from zero to full effect
- Need to define the clinically relevant level of effect – *e.g.* % reduction in liver fibrosis

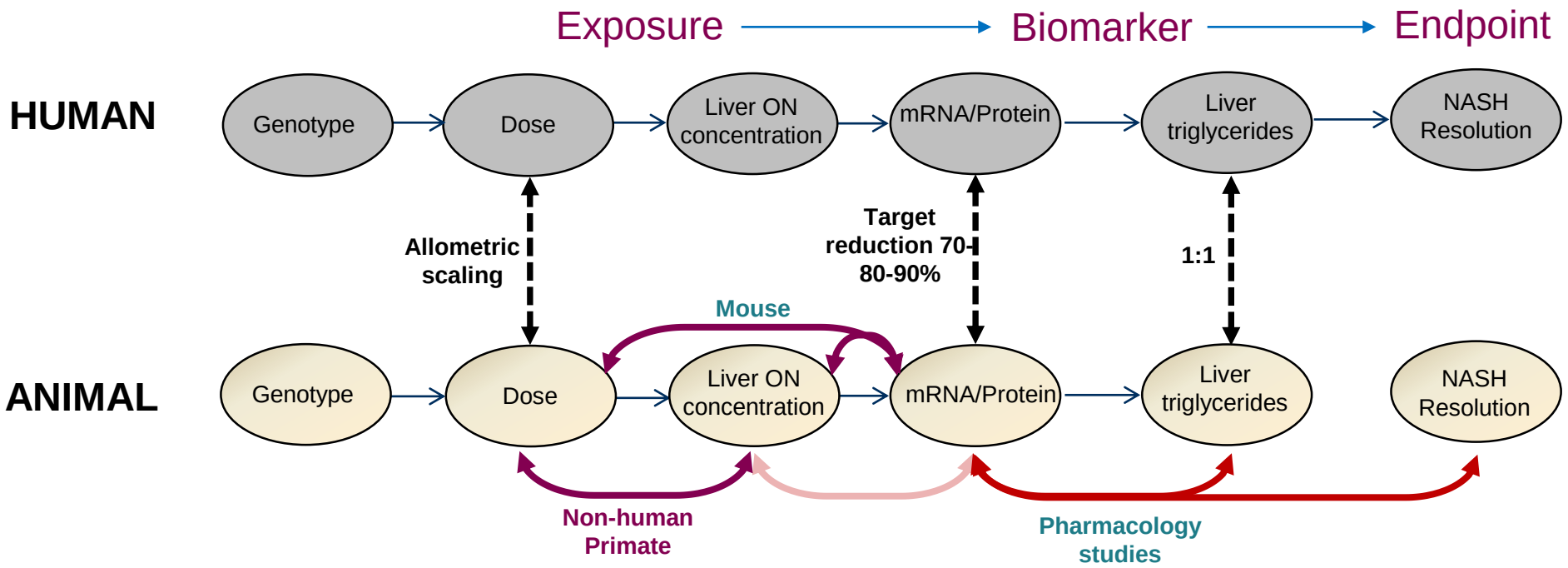
1. Define what a clinically relevant level of efficacy is
2. Translate the efficacy level to a target mRNA knock-down

Conclusions:

- Achieving sufficient in vivo exposure, at the target, the route of administration, ON half-life and potency will have an impact
- Plasma protein binding will determine the distribution and excretion of the ON and will depend on the sequence
- Time is of the essence! Half-life, Half-life, Half-life….
- Effect biomarkers can be quantitatively related to either dose or exposure

Now, how to apply this in your study designs:

Translational Map and Biomarker Strategy



Main assumptions

A. PK translates allometrically (mouse, NHP, human)
B. Liver exposure to ON with mRNA reduction in mouse translates to human
C. X% mRNA reduction in liver is enough for efficacy
D. ON half-life in human liver is assumed same as mice or 4 weeks.

Biomarker map concept adapted from: Danhof M. et al. Mechanism-based pharmacokinetic-pharmacodynamic modeling-a new classification of biomarkers. Pharm Res. 2005 Sep;22(9):1432-7.

How We use Biomarkers and Endpoints to Build Confidence in Our Compounds

Biomarker

- Continuous parameter
- May or may not be predictive of disease progression
- Onset of drug effect, **differentiation** to competitors and **dose setting** for further development
- Can be both efficacy and safety:
  e.*g.* blood pressure, uACR, HbA1c, LDL, exacerbations, neutrophil counts

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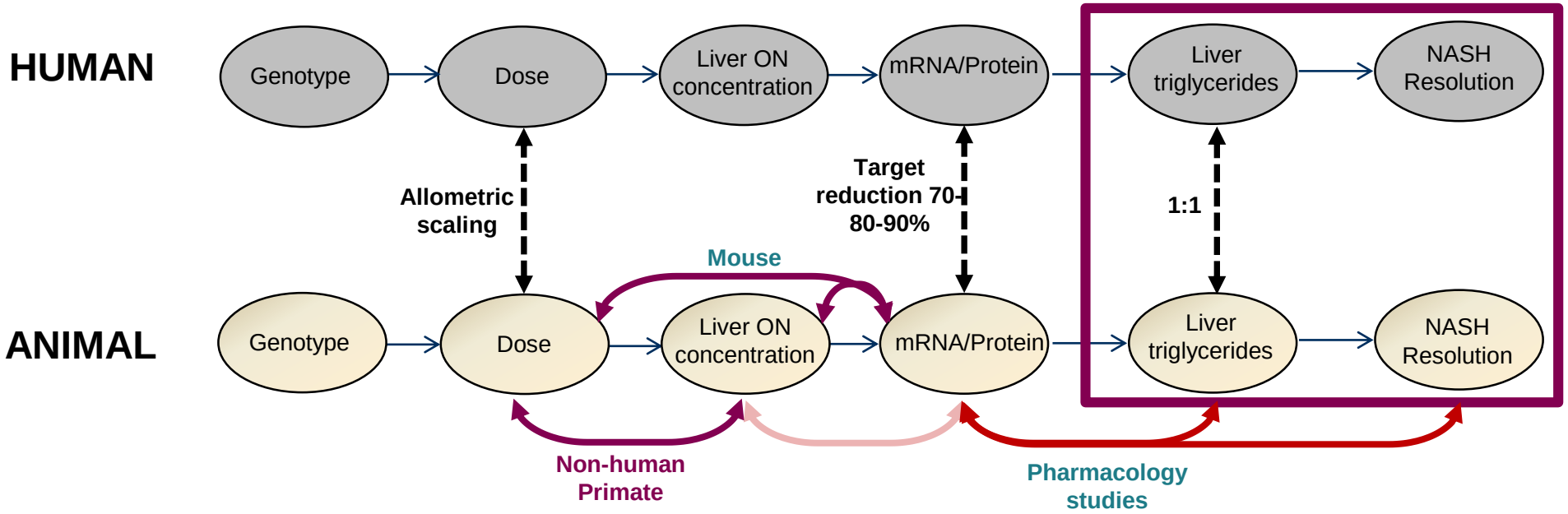
Endpoint

- A ”yes” or ”no” type measure, time to an event or frequency of events
- Predictive of disease outcome
- Used for **registration** of new drugs and indications to **claim benefit**
- Can be both efficacy and safety:
  e*g.* survival, death, prevention of myocardial infarction (MI), time to doubling of s-creatinine

Translational Map and Biomarker Strategy

Step 1: What do I need to achieve?



Main assumptions

A. PK translates allometrically (mouse, NHP, human)
B. Liver exposure to ON with mRNA reduction in transgenic mouse translates to human
C. Steady state reached in 4 week mouse study
D. X% mRNA reduction in liver is enough for efficacy
E. ON half-life in human liver is assumed same as mice or 4 weeks.

Biomarker map concept adapted from: Danhof M. et al. Mechanism-based pharmacokinetic-pharmacodynamic modeling-a new classification of biomarkers. Pharm Res. 2005 Sep;22(9):1432-7.

Regulatory Guidance Regulate the Choice of Endpoints

Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Evangela Covert 301-796-4075.

Because of the slow progression of NASH and the time required to conduct a trial that would evaluate clinical endpoints such as progression to cirrhosis or survival, the FDA recommends sponsors consider the following liver histological improvements as endpoints reasonably likely to predict clinical benefit to support accelerated approval under the regulations:[4]

- Resolution of steatohepatitis on overall histopathological reading **and** no worsening of liver fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis;

  OR

- Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) **and** no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis);

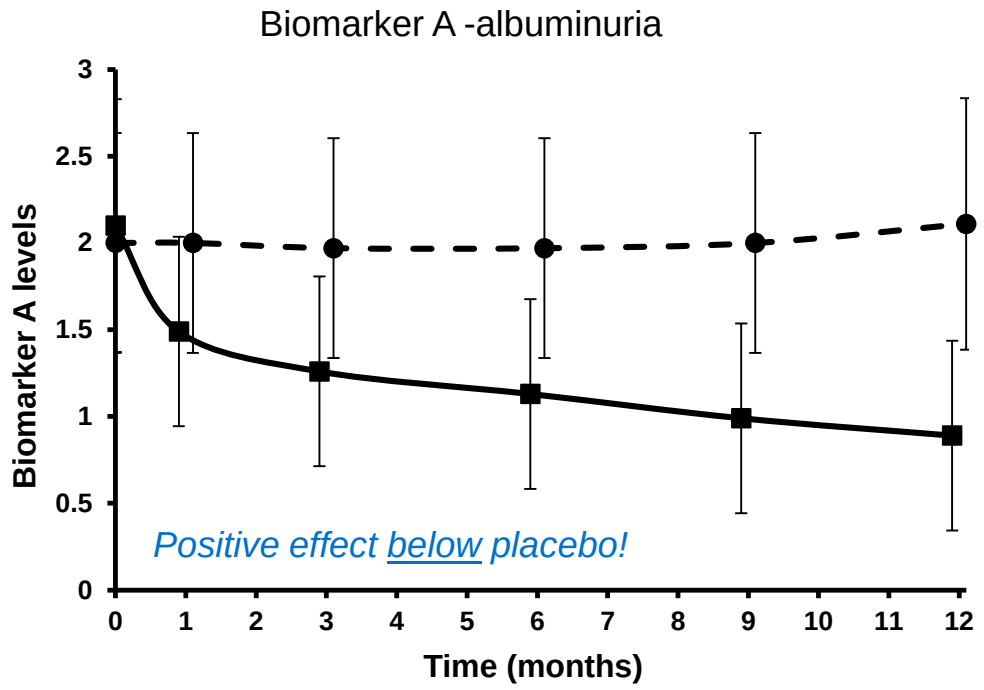
  OR

- Both resolution of steatohepatitis and improvement in fibrosis (as defined above).

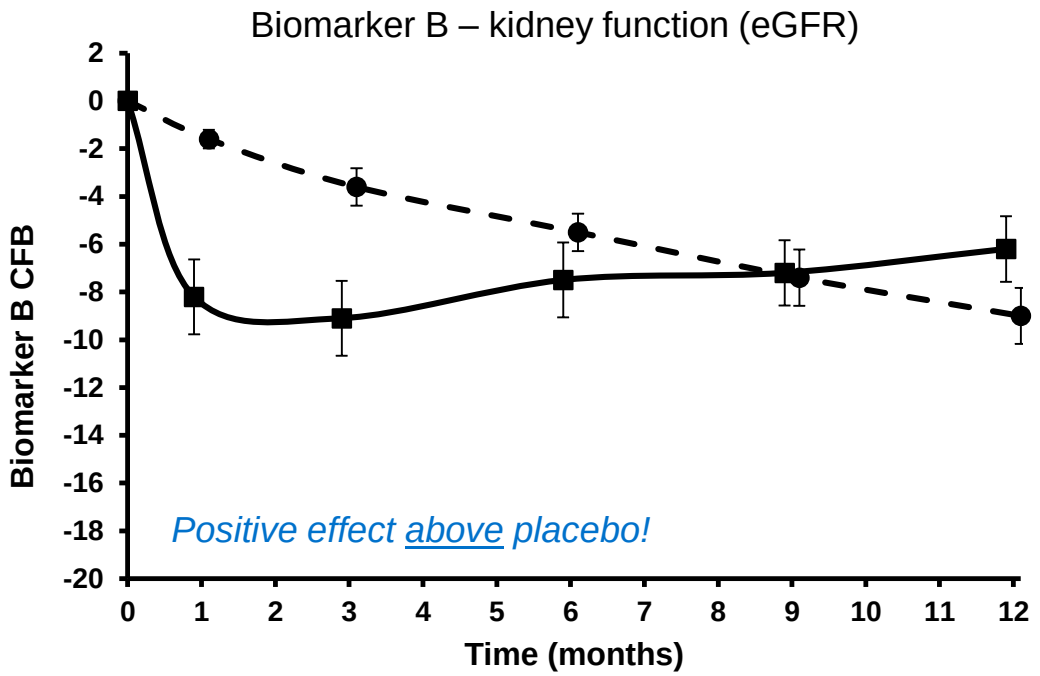
Ref: FDA Guidance on NASH, available at: https://www.fda.gov/media/119044/download, accessed 2020-01-17

Example: Predictive Biomarkers can Take Time to Show Response

Clear benefit already after 3 months



Need to study > 9 months to see benefit



(—) Drug class effect on biomarkers vs placebo (- - -)

➡ Kidney function (eGFR) is more predictive of disease progression compared to albuminuria

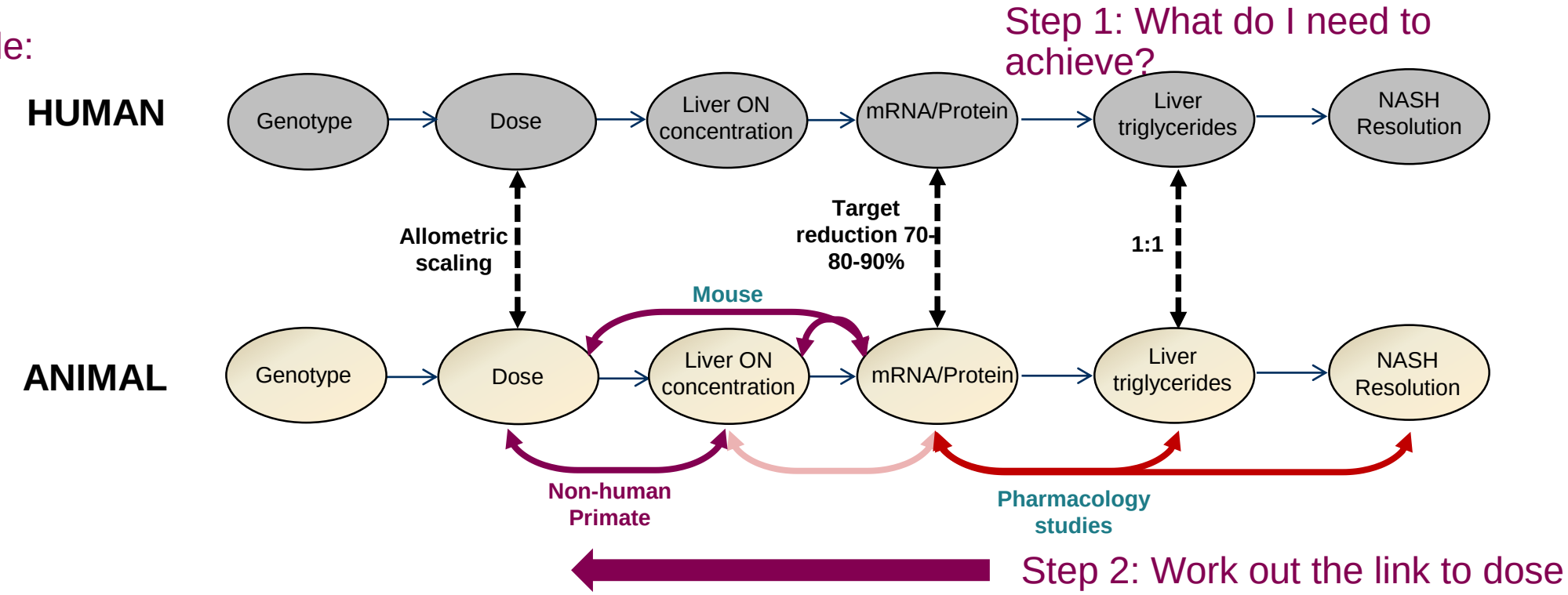
Adapted from: Bianchi S et al. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. 2006 Dec; 70 (12): 2116-2123.

The Starting Point is: What is the Driver of the Disease?

- Genetic Association vs Acquired Phenotype
- Human Target Validation – Causality or Consequence
- Population – Who is my patient and what practical and ethical aspects may there be?

Translational Map and Biomarker Strategy for NASH

Example:



Three Key Model Steps:

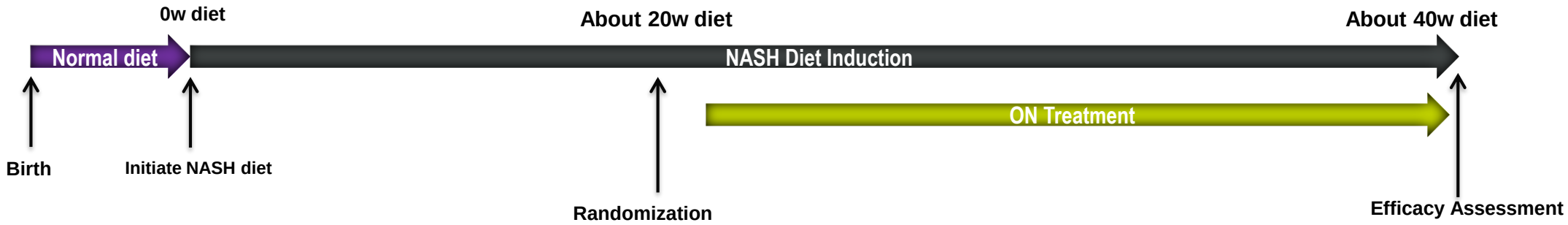
1. Pharmacology Studies
2. Mice Studies (eg. Human Transgenic)
3. Non-Human Primate Studies

Biomarker map concept adapted from: Danhof M. et al. Mechanism-based pharmacokinetic-pharmacodynamic modeling-a new classification of biomarkers. Pharm Res. 2005 Sep;22(9):1432-7.

Pharmacological Model Systems - A NASH example

To establish the link between dose, knockdown and efficacy

Example of study design:

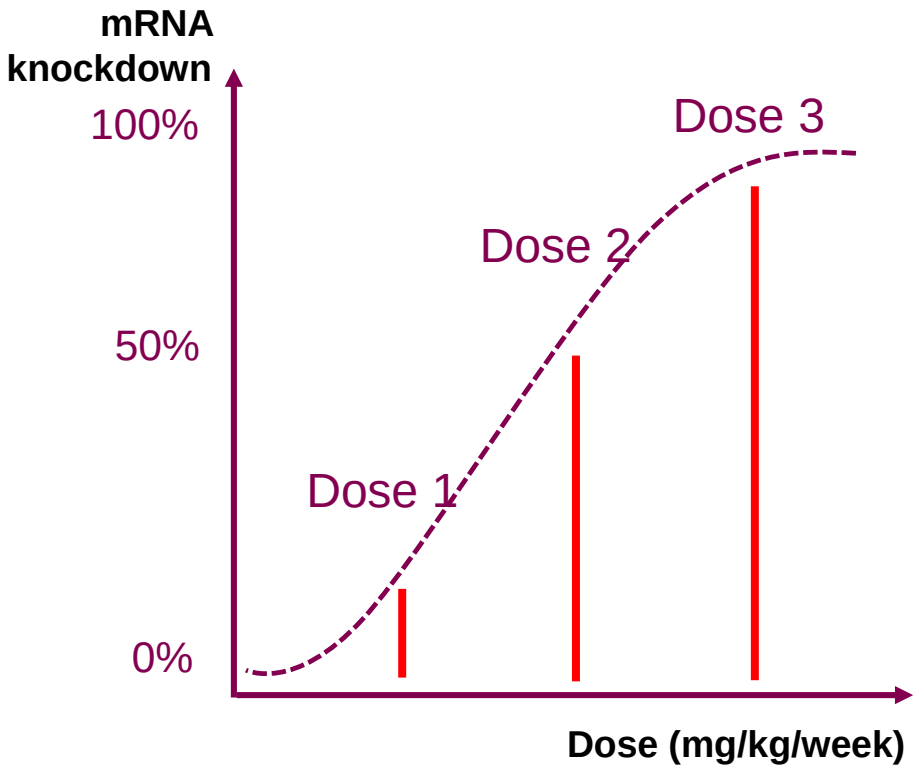


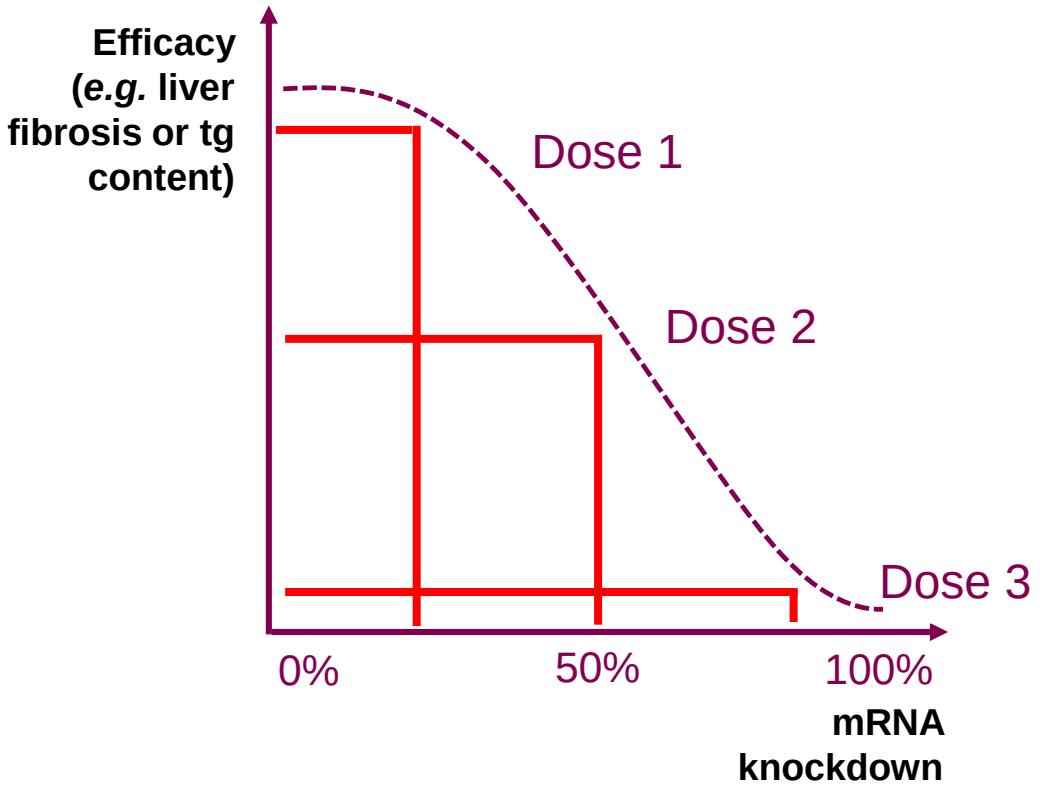
Group	Target	Dose (mg/kg/week)	# Mice
A	Control ON	Dose 3	8-10
B	Active ON	Dose 3	8-10
C	Active ON	Dose 2	8-10
D	Active ON	Dose 1	8-10
E	PBS	-	8-10

- We want to study a broad dose range to ensure to capture both no- and max effects
- Selected end-points preferably translatable to human disease resolution
- PBS and Control ASO to establish non-treatment effects

Linking Dose to Degree of Knockdown and Efficacy

We want to establish the quantitative relationship between the dose and level of knockdown to a disease modification effect



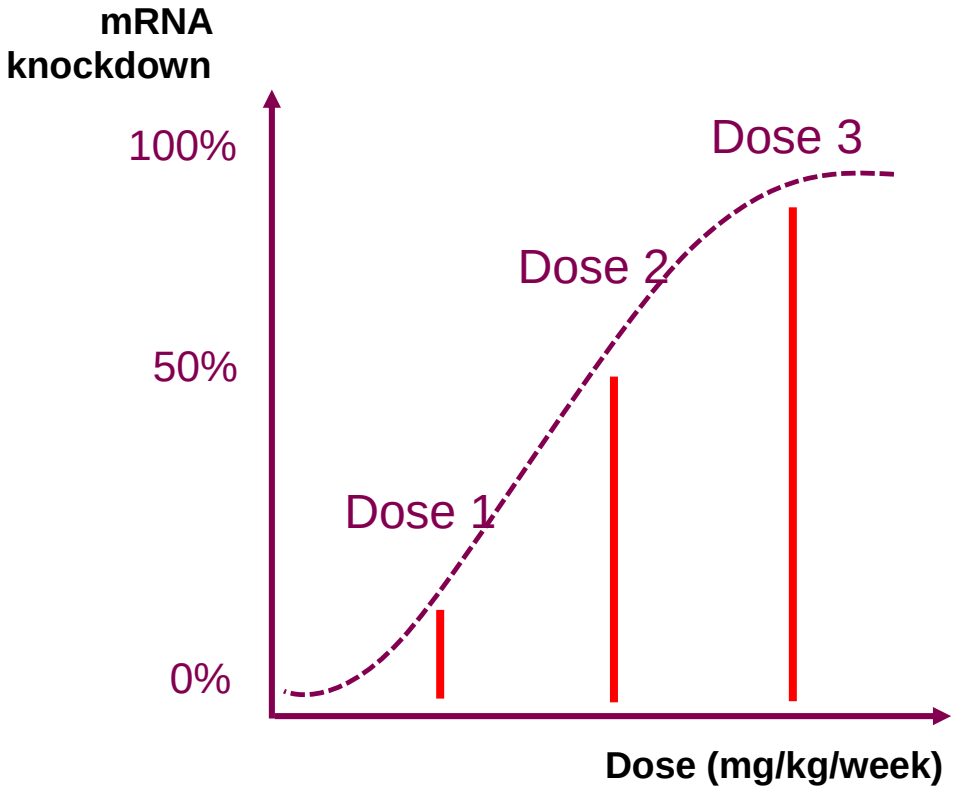


The shape of the relationship between mRNA/protein knockdown and efficacy may assume any shape

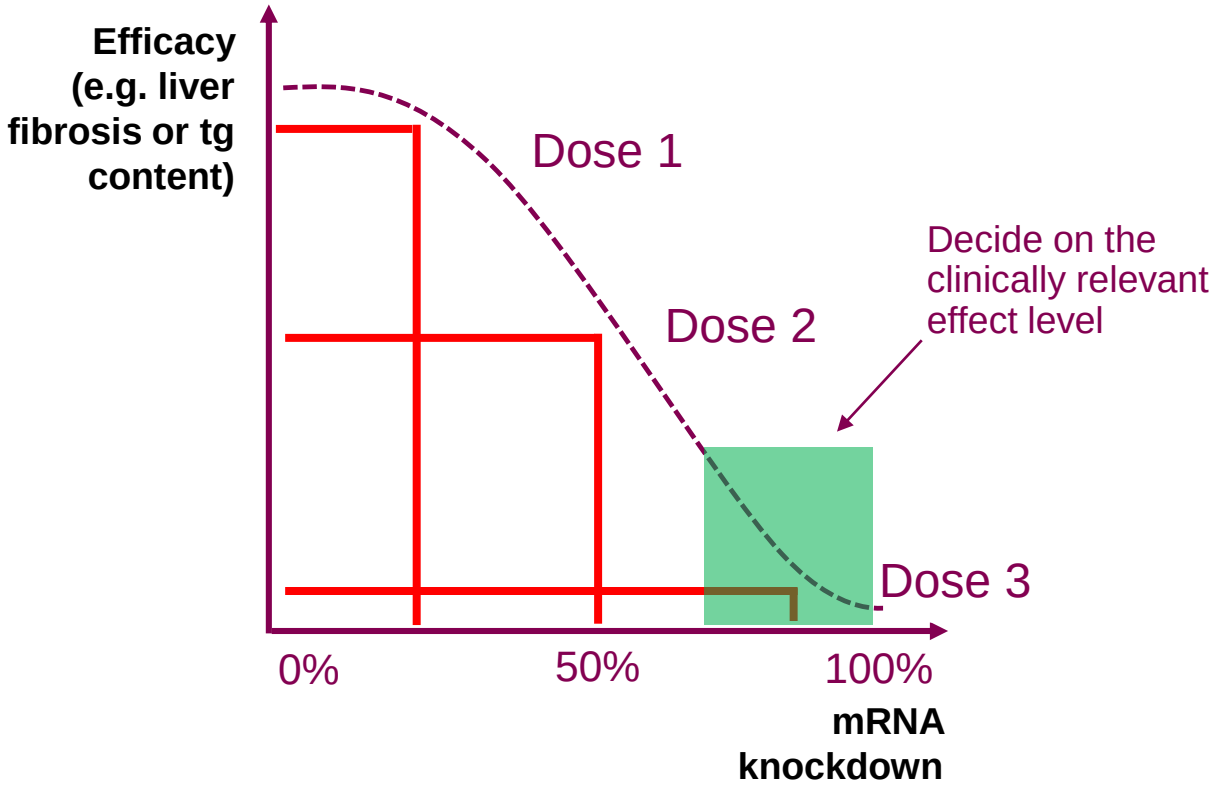
Does a targeting approach improve the efficacy of the ASO?

Linking Dose to Degree of Knockdown and Efficacy

We want to establish the quantitative relationship between the dose and level of knockdown to a disease modification effect



”To inform any subsequent studies”

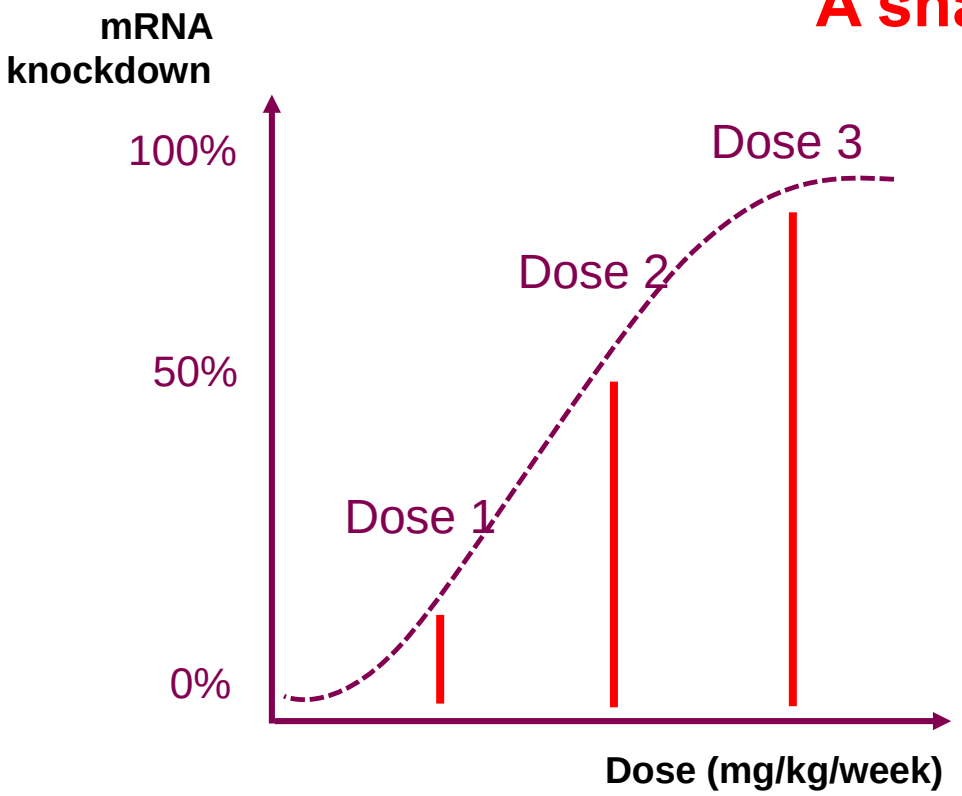


We need data to establish the link between the study end-point and a disease modifying effect in human – literature, competitors, acquired knowledge etc.…

Linking Dose to Degree of Knockdown and Efficacy

We want to establish the quantitative relationship between the dose and level of knockdown to a disease modification effect

“A snapshot in time”



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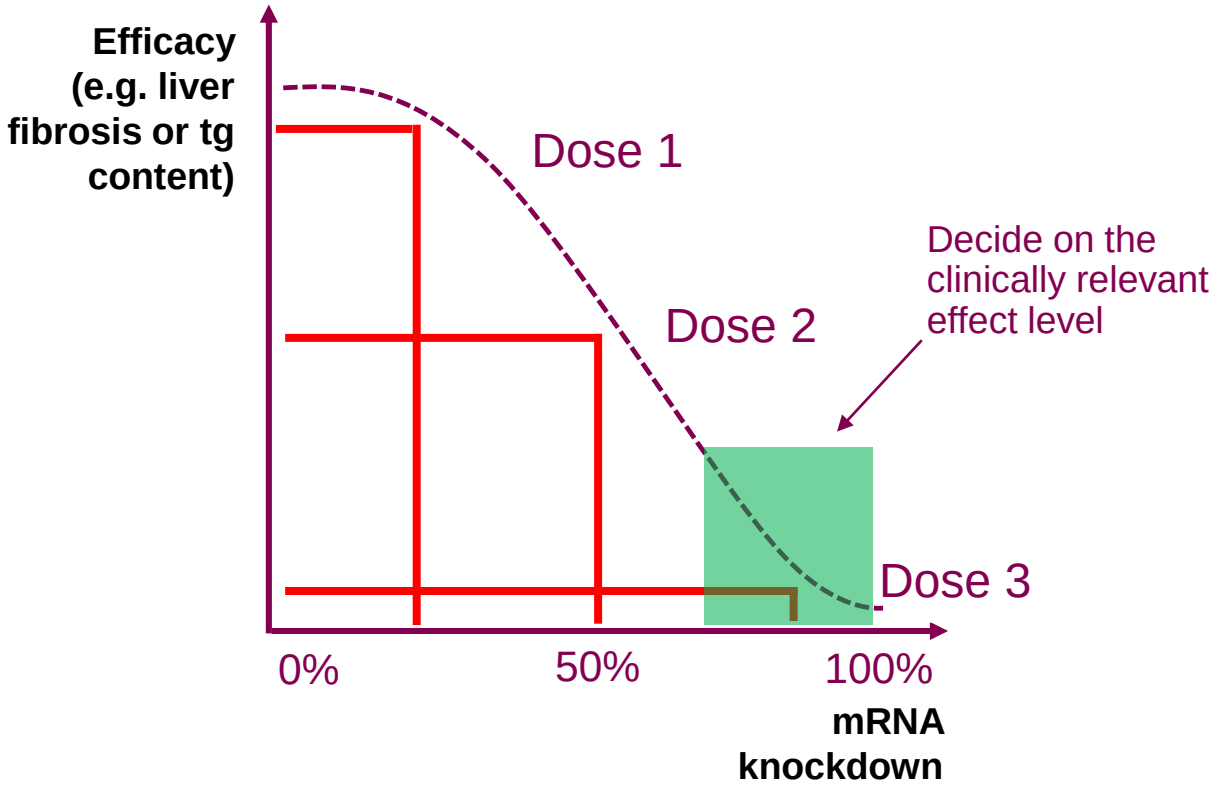

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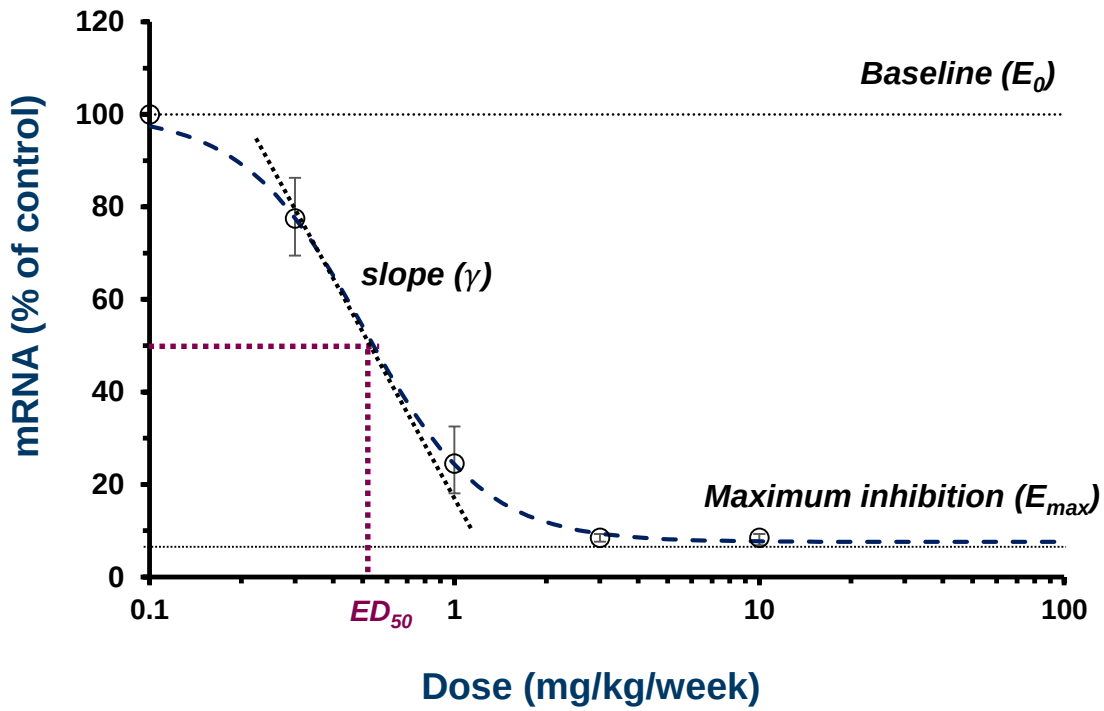
Expansion of the Exposure-Response Relationship

Repetition



E_0 is the baseline effect given by either vehicle or control (scrambled) ON

E_{max} is the maximum inhibitory (or stimulatory) effect observed; may be warranted to assume the max effect is 1 (i.e. 100% inhibition is achievable)

ED_{50} is the dose that renders 50% of the maximum effect

Slope is the slope of the relationship
low value – flat relationship
high value – steep relationship (on/off)

$$E = E_0 - \frac{E_{max} \times Dose^{\gamma}}{ED_{50}^{\gamma} + Dose^{\gamma}}$$

"Absolute inhibition"

$$E = E_0 \left(1 - \frac{E_{max} \times Dose^{\gamma}}{ED_{50}^{\gamma} + Dose^{\gamma}}\right)$$

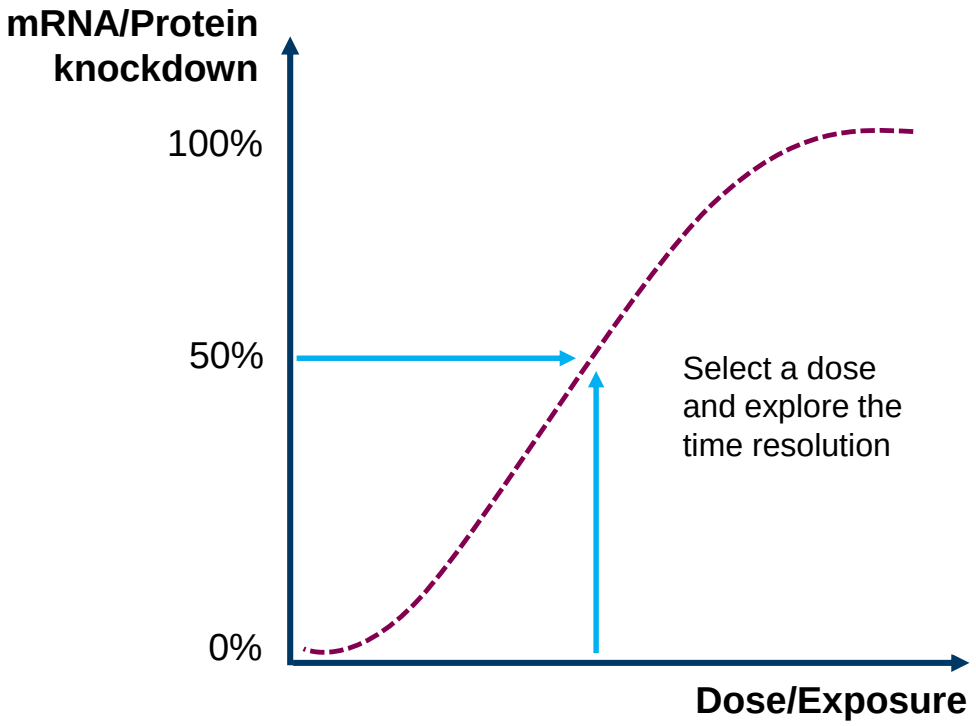
"Relative inhibition"

Figure and equations adapted from Olof Gissberg et al. (eds.), Oligonucleotide-Based Therapies: Methods and Protocols, Methods in Molecular Biology, vol. 2036,Springer Nature 2019

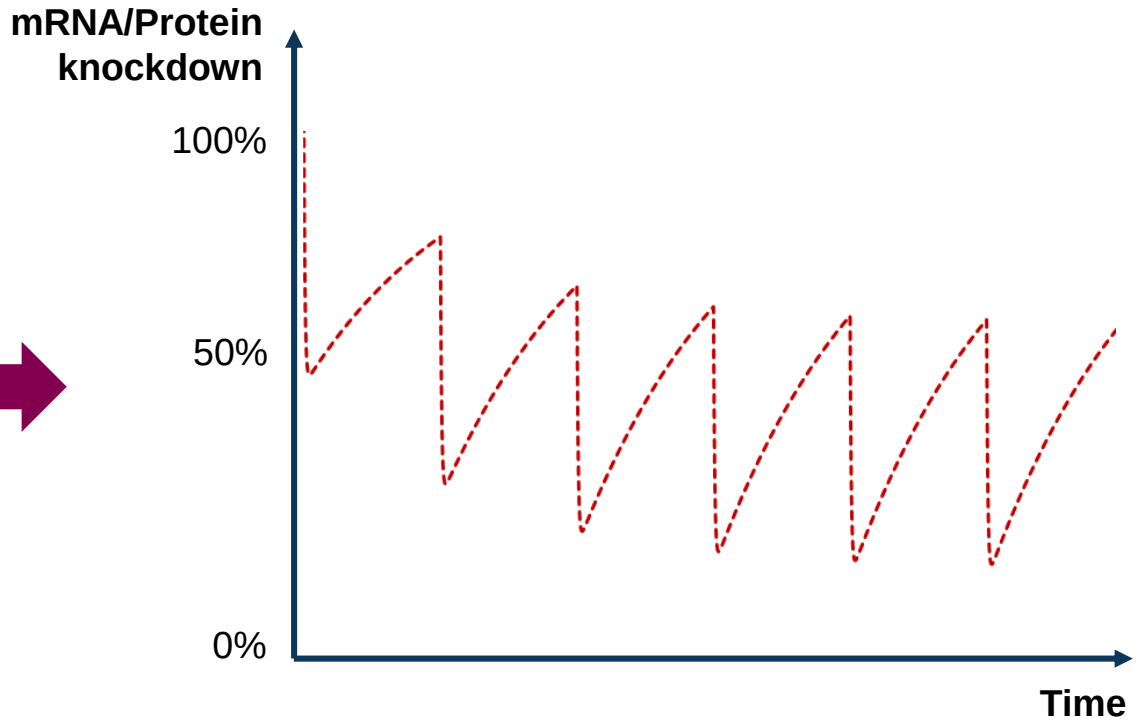
Time is an Important Component also for Effect

Repetition

"Snapshot in time"



Multiple doses – accumulation of effect

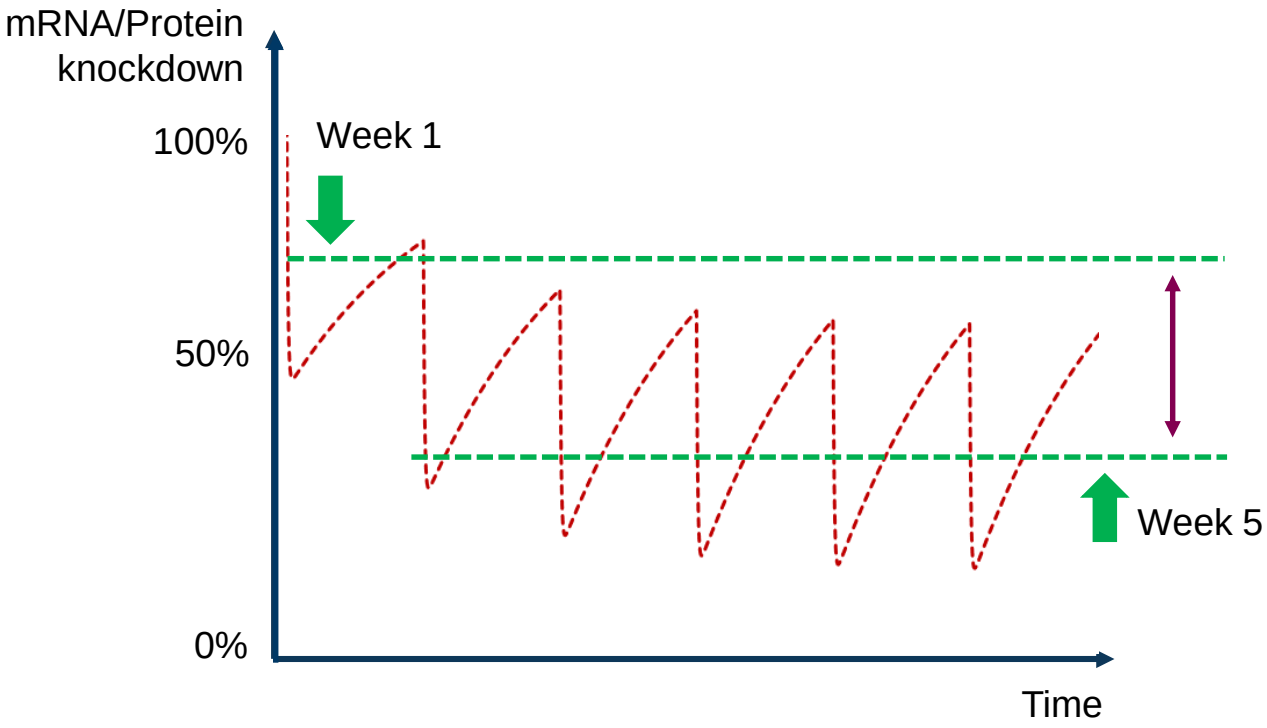


Accumulation of effect over time, depending on either: drug exposure acc. or **the effect half-life**

Pharmacodynamics – "What the Drug Does to the Body"

Repetition

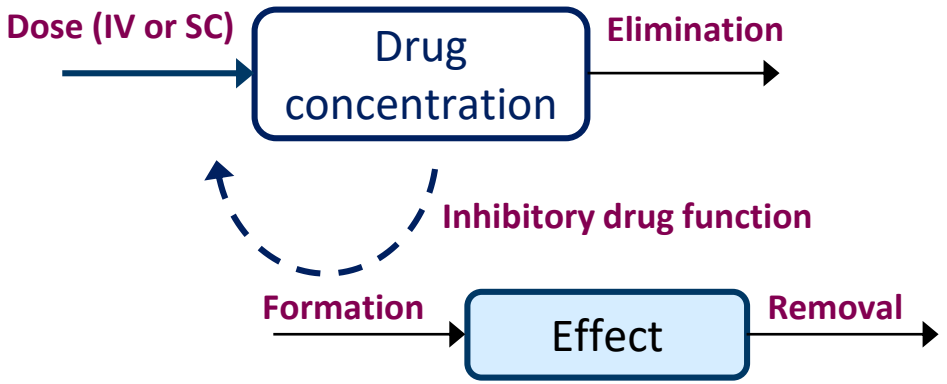
Multiple doses – accumulation of effect



PD $t_{1/2}$ time to reach 50% of the maximum effect

Onset/offset how fast the effect initially comes and for how long the duration is

To link exposure and effect over time we can use an indirect response model:

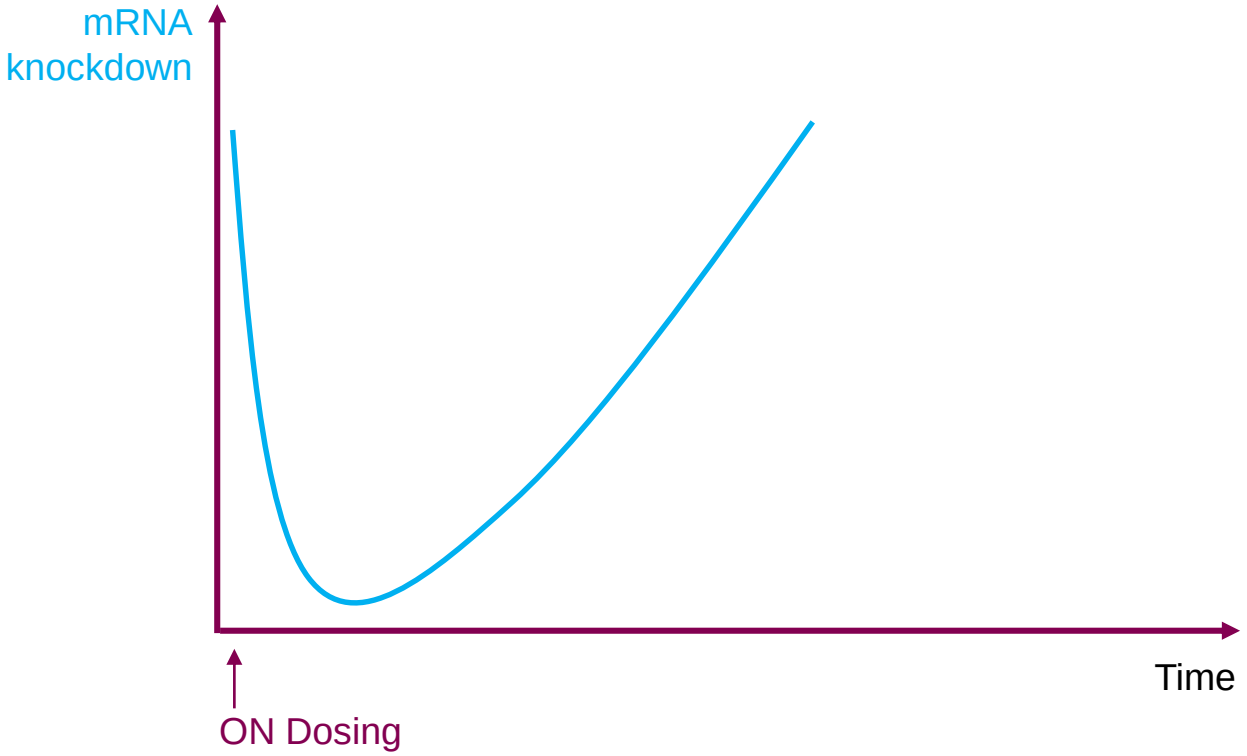


where both the time course of the ON and the effect are taken into account

Model figure adapted from Olof Gissberg et al. (eds.), Oligonucleotide-Based Therapies: Methods and Protocols, Methods in Molecular Biology, vol. 2036,Springer Nature 2019

Time is of the Essence – When and What to Measure?

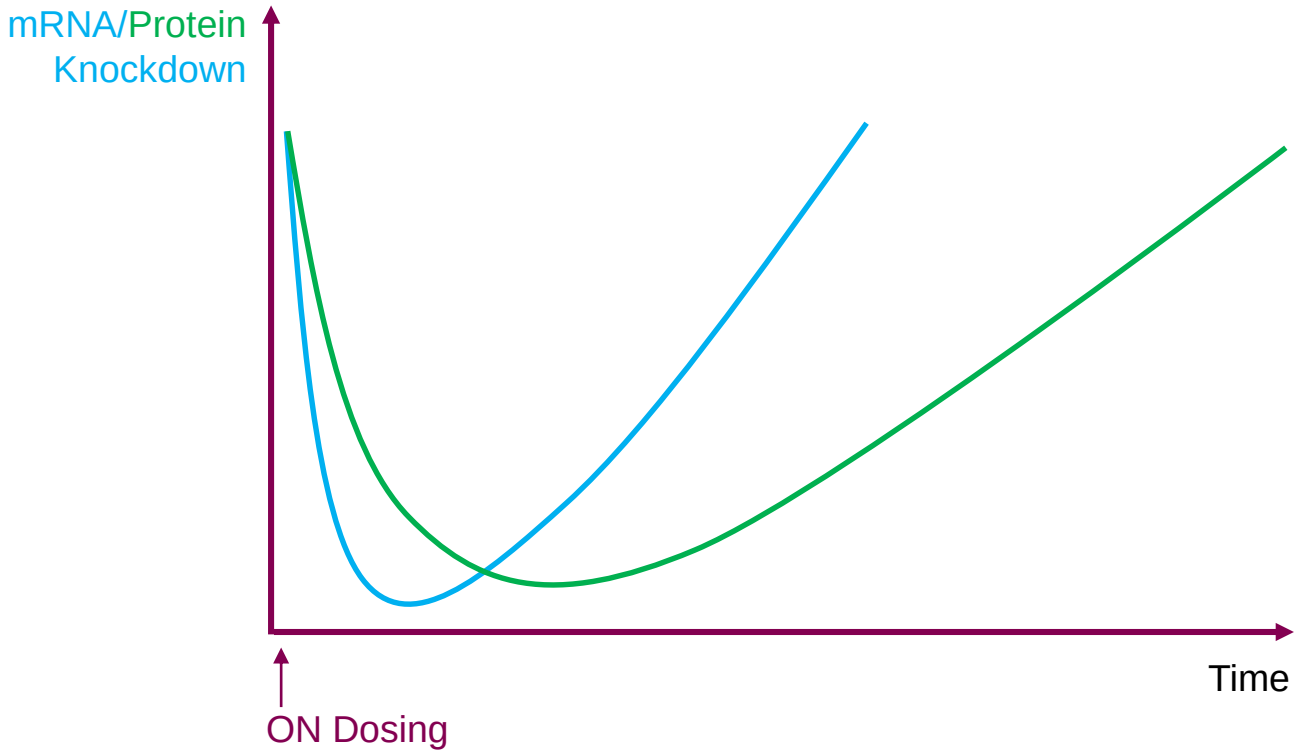
Onset and magnitude of effect is crucial information for designing your study



- mRNA is usually quick to onset and diminishes with the same rapid offset protein is generally slightly slower in on- and offset
- Translate the efficacy level to a target mRNA knock-down

Time is of the Essence – When and What to Measure?

Onset and magnitude of effect is crucial information for designing your study



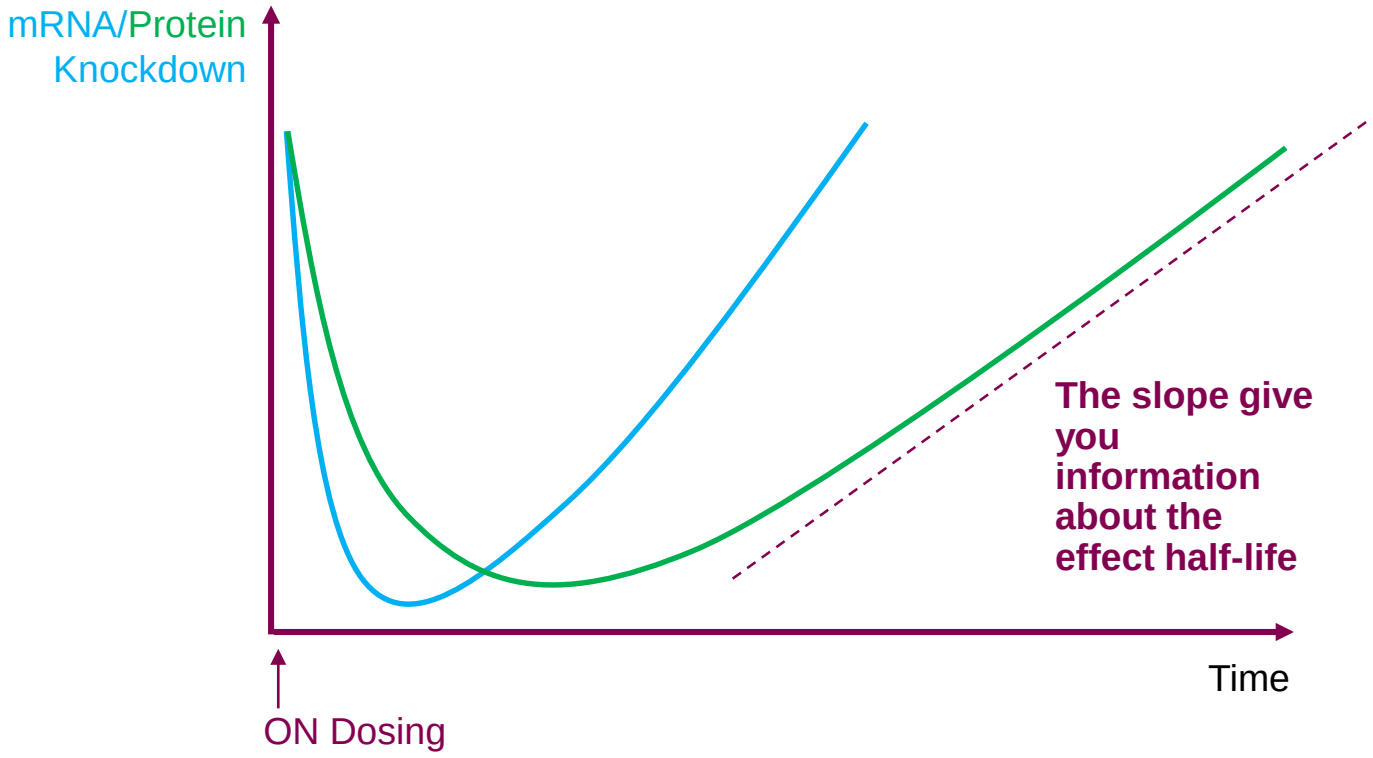
- It is important to understand the time component for when the different effects kick-in and when to expect to see the results
- To give information on the time-resolution of effects, collecting data also after stopping treatment is very important
- The time-resolution will inform PKPD modeling efforts to make predictions of when and how much effect that can be expected

1. mRNA is usually quick to onset and diminishes with the same rapid offset protein is generally slightly slower in on- and offset

2. Downstream response biomarker effects takes longer time to develop

PKPD to Inform Selection of Biomarkers

Onset and magnitude of effect is crucial information for designing your study



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Understanding the time to onset of effect will inform if steady-state conditions apply or not (3-5x effect half-life)

If assessments are made at non-steady-state condition this may lead to underestimations of the true effect – loading dose scheme may help to reach steady-state quicker

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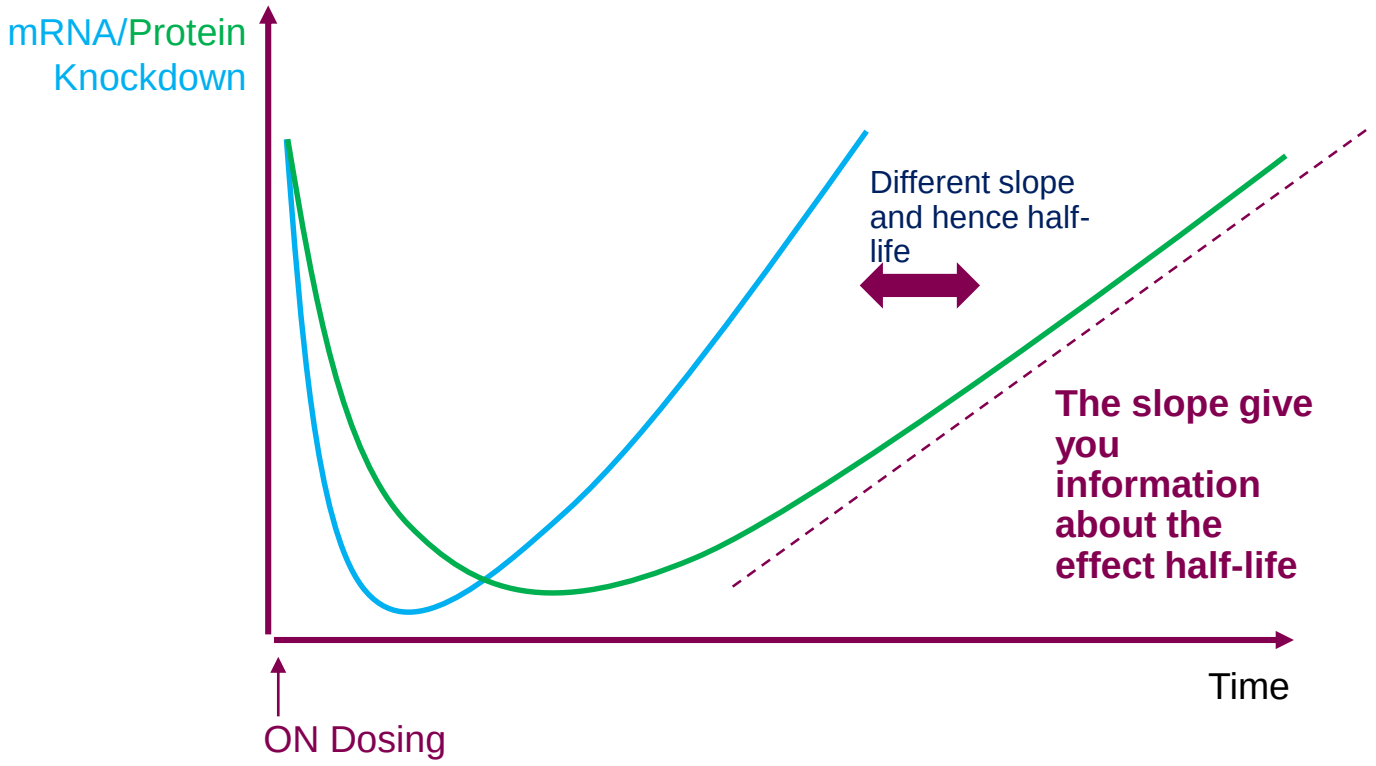

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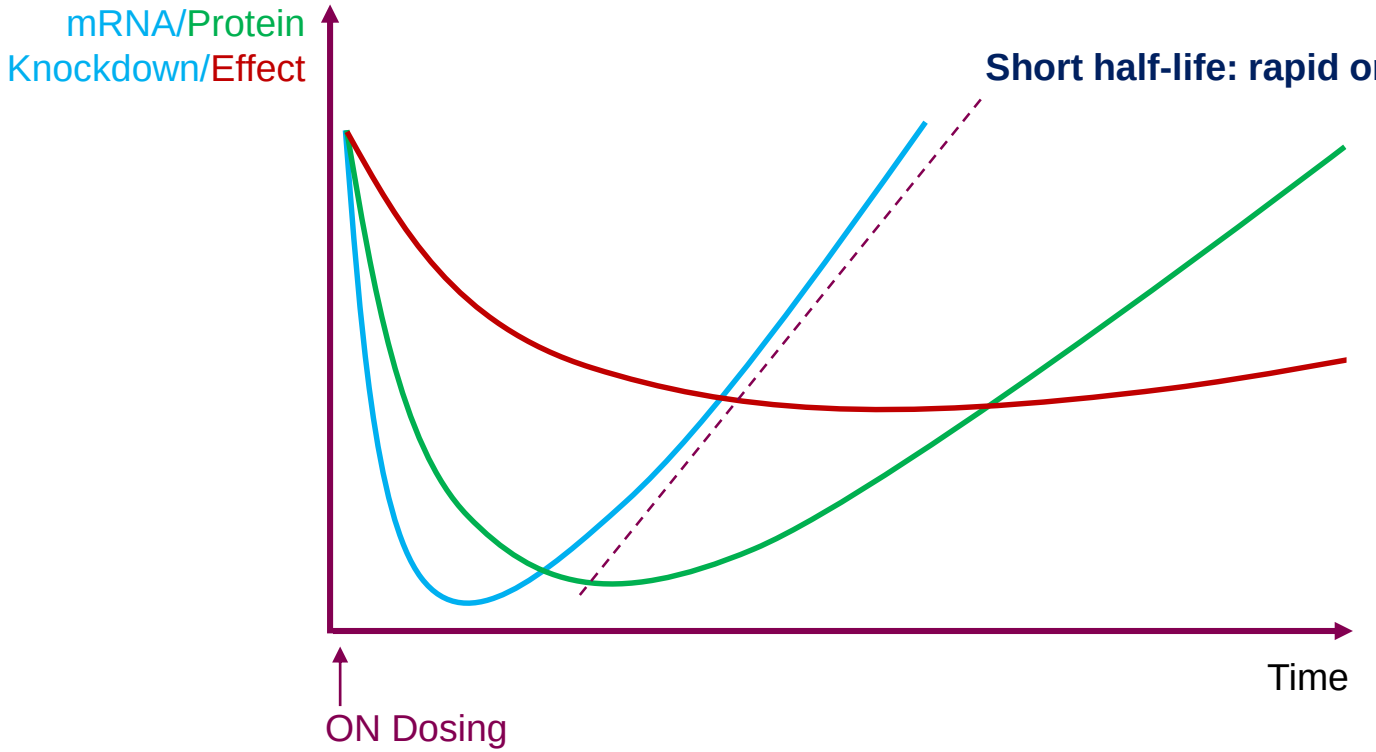


Three alternative biomarkers to measure
– which to select?

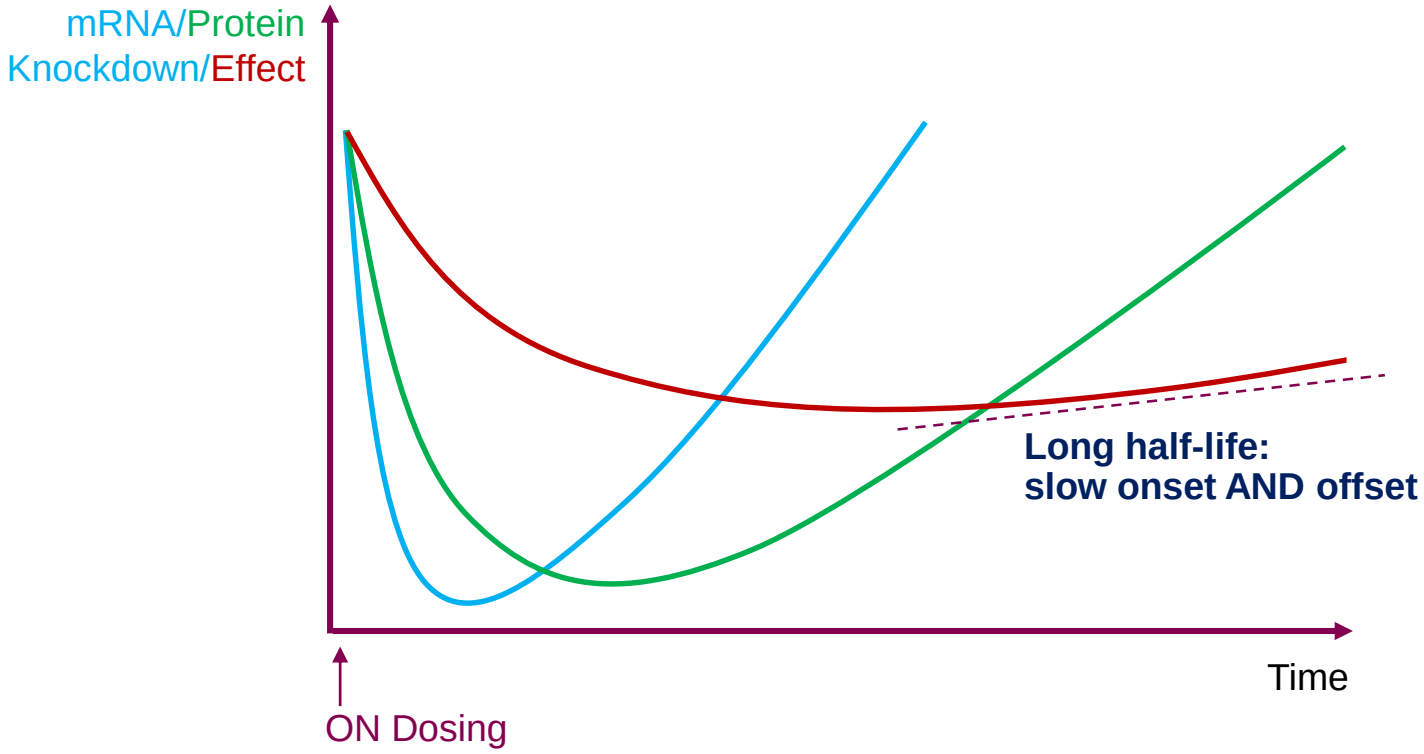
Establish the quantitative relationship with focus on onset/offset and magnitude of effect

How long can we run the study/assay for?
- technical/feasible and ethical consideration

Sampling also during the recovery phase to collect ”return to baseline” will give you important information on the effect half-life – you may need recovery groups for this.

Time is of the Essence – When and What to Measure?

Onset and magnitude of effect is crucial information for designing your study



Three alternative biomarkers to measure – which to select?

Establish the quantitative relationship with focus on onset/offset and magnitude of effect

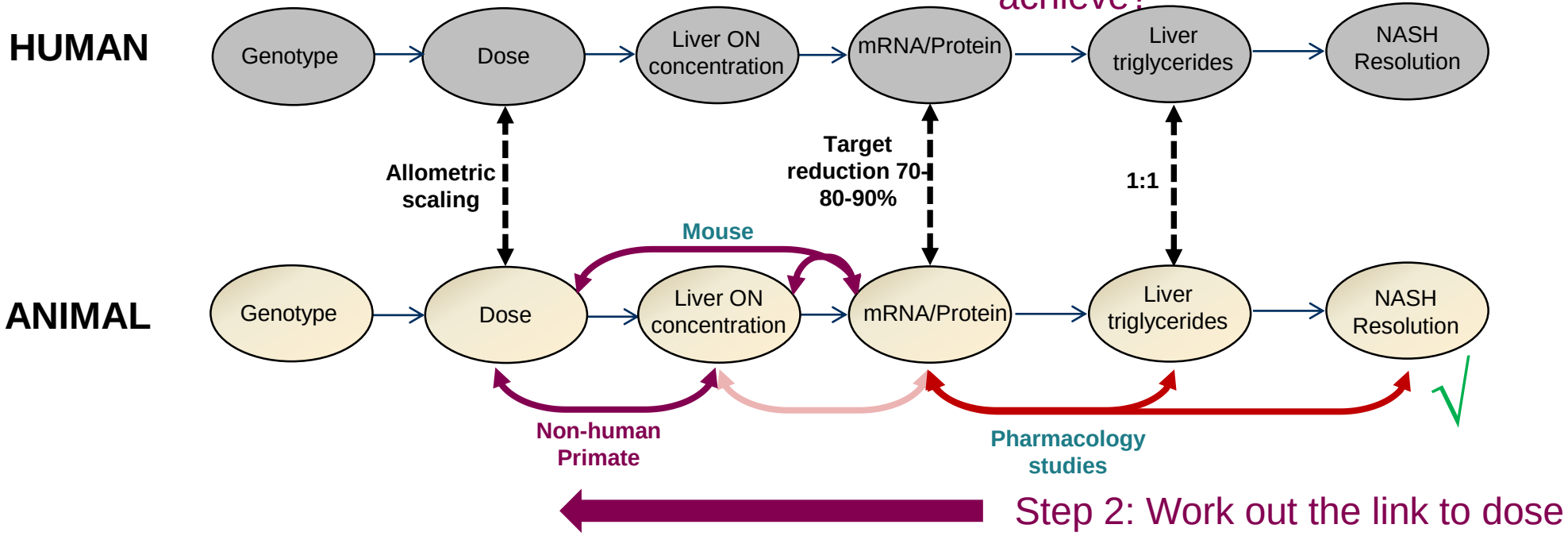
If your effect half-life is long enough the PK will not impact the effect duration

Loading doses may reduce time to steady-state levels

Translational Map and Biomarker Strategy for NASH

Example:

Step 1: What do I need to achieve?



Three Key Model Steps:

1. Pharmacology Studies √
2. Mice Studies (eg. Human Transgenic)
3. Non-Human Primate Studies

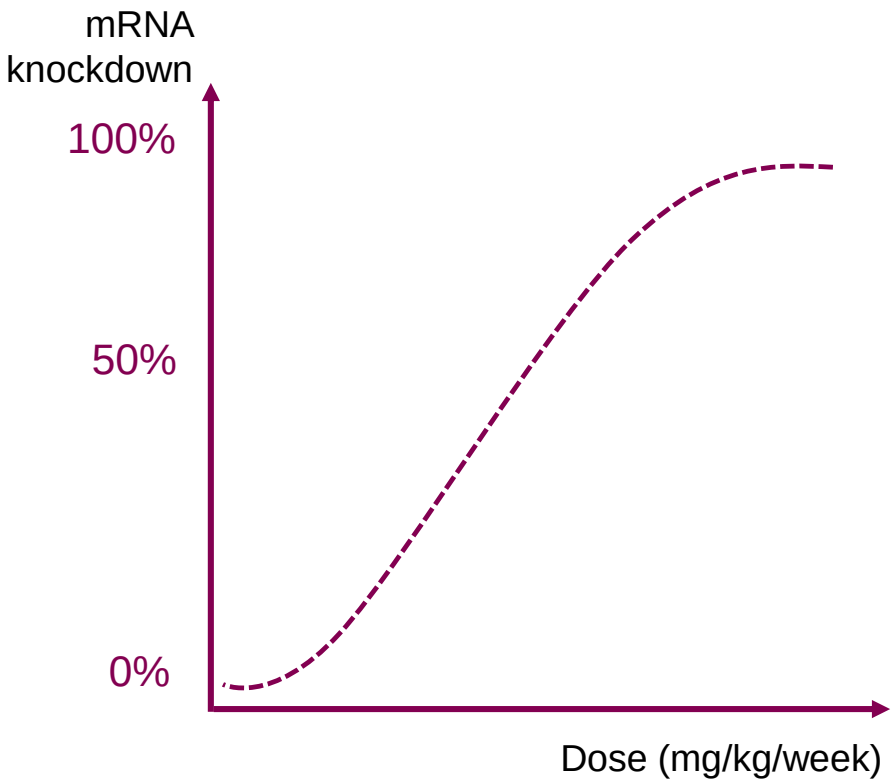
Biomarker map concept adapted from: Danhof M. et al. Mechanism-based pharmacokinetic-pharmacodynamic modeling-a new classification of biomarkers. Pharm Res. 2005 Sep;22(9):1432-7.

Establishing the Potency of the Human Candidate ON

Why can we not use the mouse data generated in the pharmacology study for potency?

Establishing the Potency of the Human Candidate ON

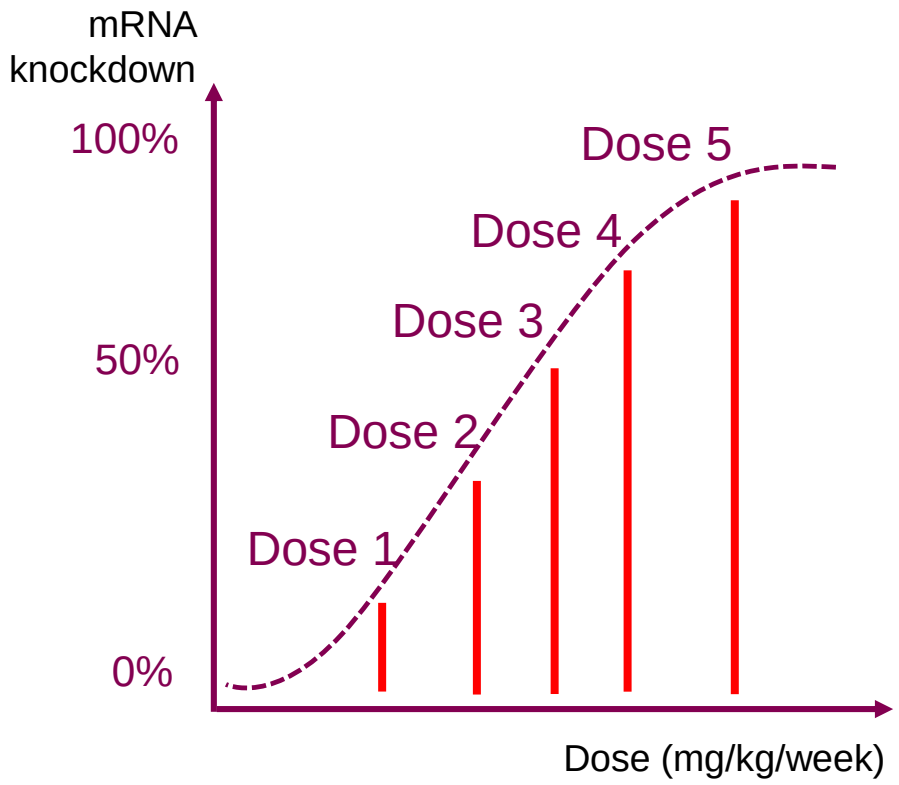
The potency of human candidates can be evaluated in transgenic mice



- Need a transgenic mouse strain to get potency on human candidates (*e.g.* homozygote vs heterozygote)
- When steady-state conditions apply either dose-response or exposure-response can be used for assessing potency
- Typical study time is four weeks and terminal measurements of: target organ knockdown (and exposure)
- To mitigate any uncertainty – use exposure as this is not sensitive to the steady-state assumption

Establishing the Potency of the Human Candidate ON

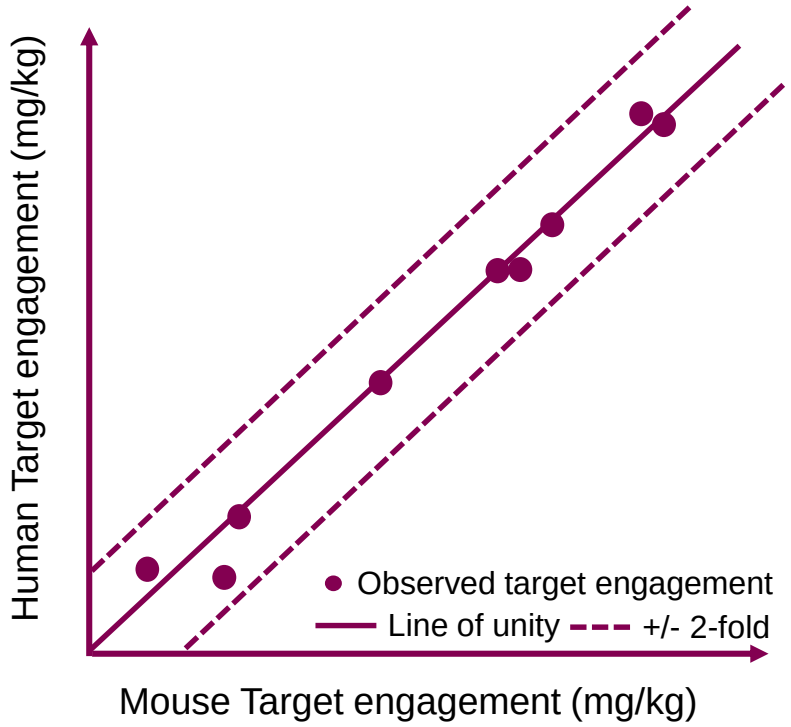
The potency of human candidates can be evaluated in transgenic mice



- The ON screening data generated in the screen can be used to inform dose selection
- Distribute your dose levels high/low and around the IC_{50} for best precision in the estimate
- For non-conjugated ONs and situations where higher precision in the dose estimate is needed, 5-dose levels in your dose response study will likely increase the precision in your potency estimate (IC_{50})

Translating the Derived Mouse Potency to Human

Using the established relationship between human and mouse potency



Summary of publicly available observed data from ON in development

- There is an established correlation between mouse and human target engagement published by Andersson et al.
- Currently, most information is available for liver targets but apparently no difference between conjugated an unconjugated ONs
- Emerging therapies will be included when available to improve the translations also for other (non-hepatic) indications

Figure schematically adapted from: Andersson S et al. Drug metabolism and pharmacokinetic strategies for oligonucleotide- and mRNA-based drug development. Drug Discov Today 2018 Oct;23(10):1733-1745

Translational Map and Biomarker Strategy for NASH

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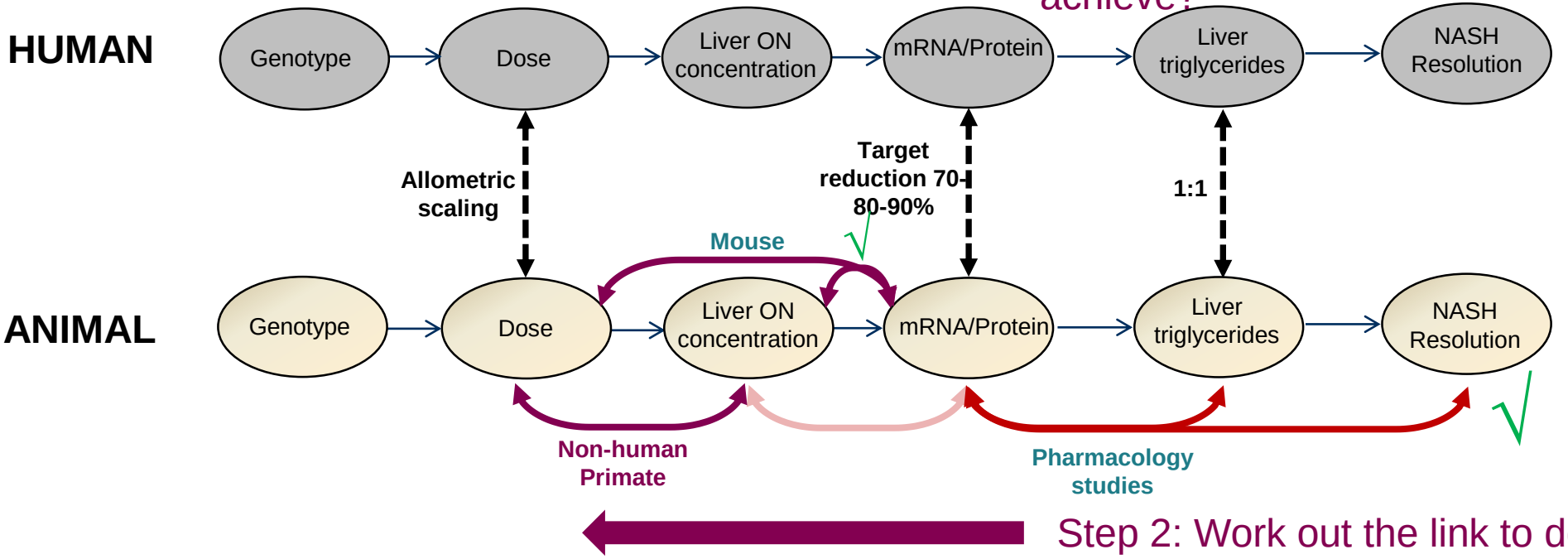

Step 2: Work out the link to dose

Three Key Model Steps:

1. Pharmacology Studies
2. Mice Studies (eg. Human Transgenic)
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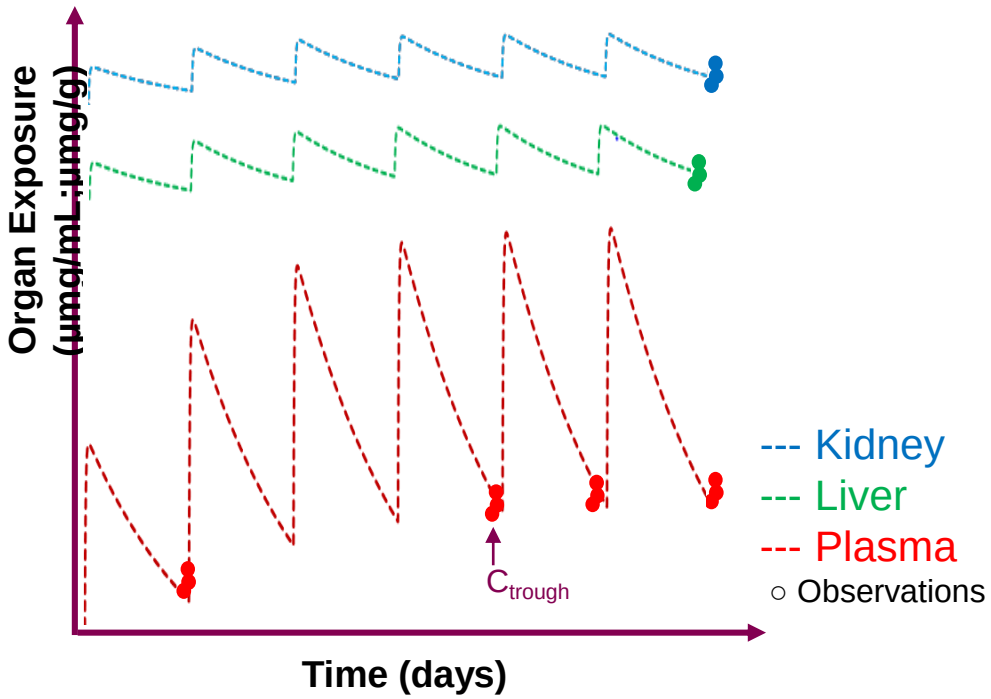
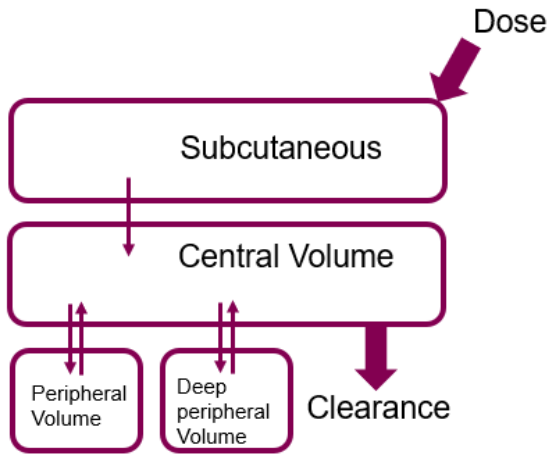
Step 2.5: Establish your PK profile

Non-human Primate PK and Tolerability Screen

The tolerability of the ON candidates can be investigated in a non-human primate screen study



- Weekly dosing (for 12 weeks) at a high dose level with the final human candidates
- To assess safety and tolerability of the candidates
- Repeated plasma samples and terminal organ exposure are collected to inform mathematical PK modelling
- Model simulations can be made to test different dosing and administration scenarios:



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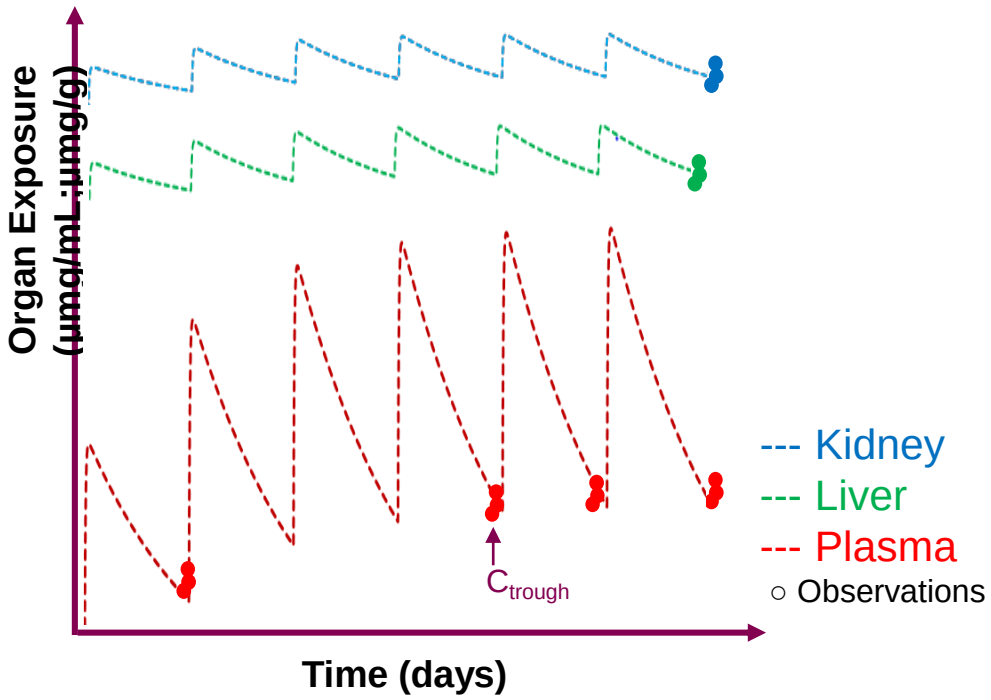

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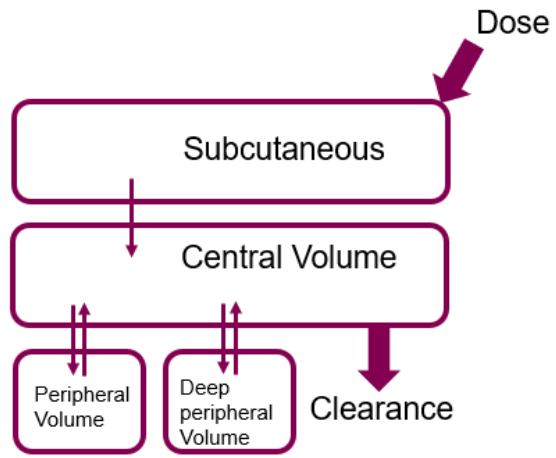
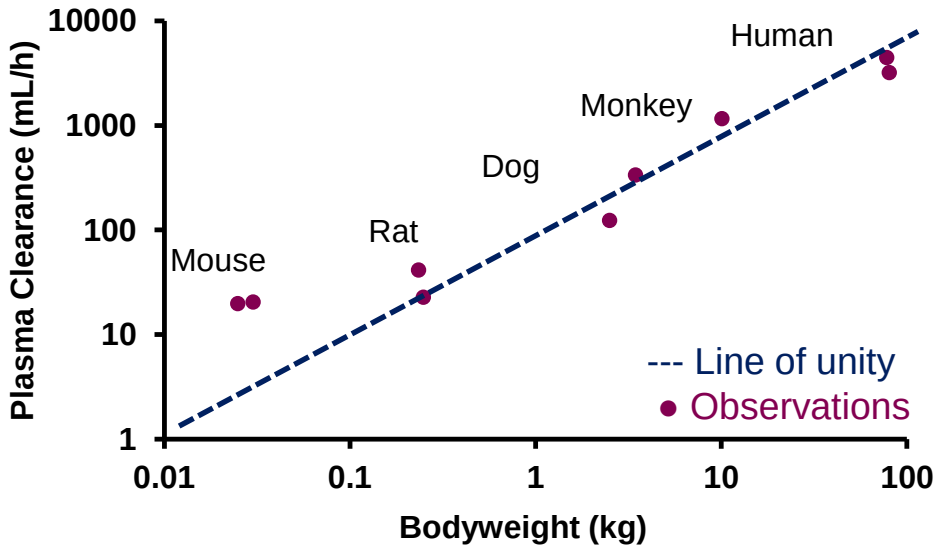


Does enough of the ON distribute to the target organ in relation to the potency to enable a clinically relevant effects in humans?

Scaling of ASO PK Parameters Between Species

The metabolic capacity across different species is related to bodyweight



- The PK parameters can be scaled to human from preclinical species according to allometric priciples
- Your may have more than one species to scale from – choose average or “highest” animal?
- Mouse may deviate from the presented relationship

$$CL_i = CL_{std} \times \left(\frac{Bodyweight_i}{Bodyweight_{std}} \right)^{3/4}$$

i = species scaling to
std = species scaling from

Ref: Yu et al. DMD, 2007. 35(3): 460-468; Geary et al. DMD 2003. 31(11): 1419-1428

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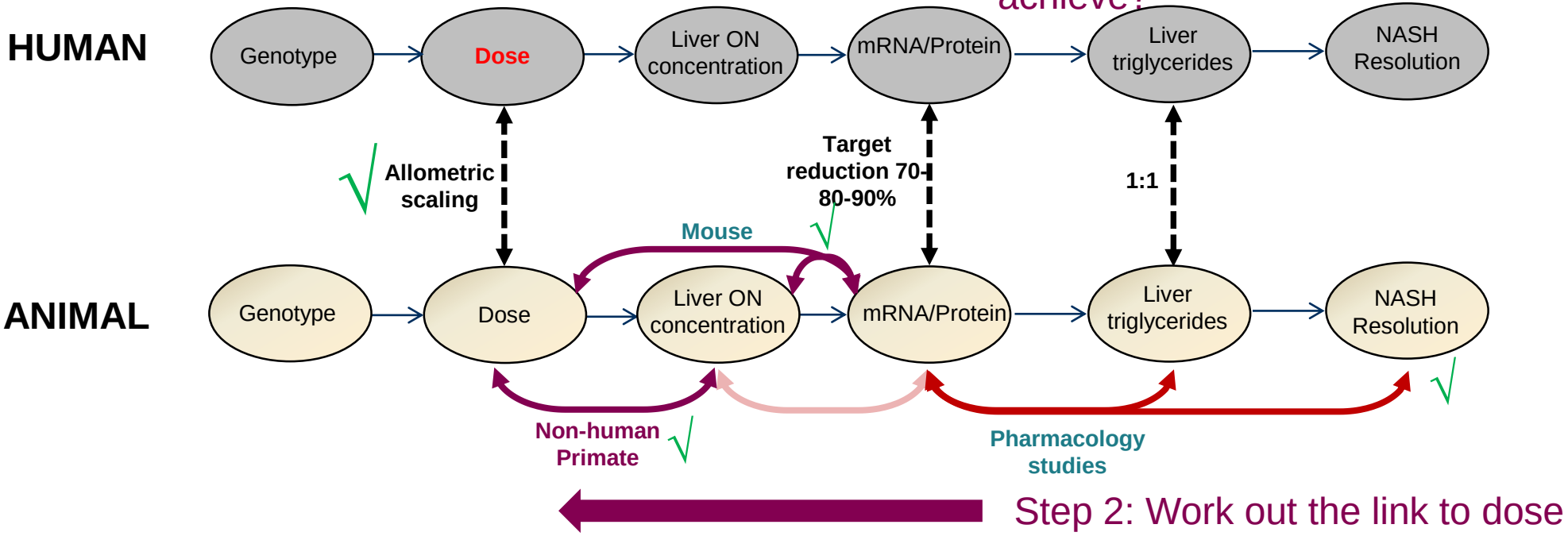

Step 2: Work out the link to dose

Three Key Model Steps:

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Conclusions:

- ONs are thoroughly screened to ensure safety and efficacy
- A biomarker map will help you in developing your ON drug and structures the biomarkers and endpoints that you need to show effect on
- The time component is important both for your efficacy and potency studies as this may impact your assessments
- Appropriate controls, both vehicle and scrambles ONs are encouraged to include in studies to determine the “true” effect
- Increasing the number of dose groups in your dose-response studies may increase the precision in your potency assessment if needed
- Scaling principles can be applied for PK to derive the predicted dose in man

Thank you!

Acknowledgements:

Rasmus Jansson-Löfmark

Shalini Andersson

Marie Elebring

Anders Dahlén