Characteristics of **therapeutic mAbs and small molecules**

Small-molecule drugs are **small chemical entities** and therapeutic mAbs are **complex proteins** with **high target specificity**[1,2]

DISCOVER

Unlike some small molecules, therapeutic mAbs **do not readily cross the blood-brain barrier** and therefore have minimal distribution in the CNS[2]

DISCOVER

Therapeutic mAbs have **a longer half-life** than small molecules, which may lead to **longer dosing intervals**[2,3]

DISCOVER

Safety considerations for small molecules may include **drug-drug interactions**[4]

DISCOVER

Safety considerations for therapeutic mAbs may include **immunogenicity and on-target effects**[2]

DISCOVER

CNS, central nervous system; mAb, monoclonal antibody.

1. Zhao L, et al. *Acta Pharmacol Sin*. 2012;33:1339-1347. **2.** Foltz IN, et al. *Circulation*. 2013;127:2222-2230. **3.** Silberstein S, et al. *Headache*. 2015;55:1171-1182. **4.** Serra López-Matencio JM, et al. *J Immunol Sci*. 2018;2:4-7.

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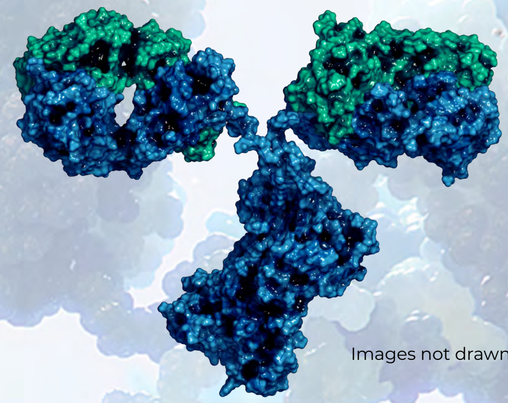
Therapeutic mAbs Differ From Small-Molecule Drugs in Size and Target Specificity[1,2]



Images not drawn to scale.

	Small molecule	Therapeutic mAb
Therapy type[1]	Chemical entity	Biologic*
Production[2]	Chemical synthesis; relatively easily controlled	Purification from cell culture media; more complex
Size[2]	~0.5 kDa	~150 kDa
Complexity[3]	Structurally less complex	Structurally more complex
Target[2]	Intracellular or extracellular	Extracellular
Specificity[2]	Lower	High
Crossing the blood-brain barrier[2]	More likely	Minimal

mAb, monoclonal antibody.
*Biologics are large, complex molecules produced in living systems that are used to diagnose, prevent, treat, and cure medical conditions.[4]

1. Zhao L, et al. *Acta Pharmacol Sin*. 2012;33:1339-1347. **2.** Foltz IN, et al. *Circulation*. 2013;127:2222-2230. **3.** Kleinberg M, et al. *Am J Health Syst Pharm*. 2004;61:695-710.
4. FDA. www.fda.gov/media/108557/download. Accessed October 24, 2019.

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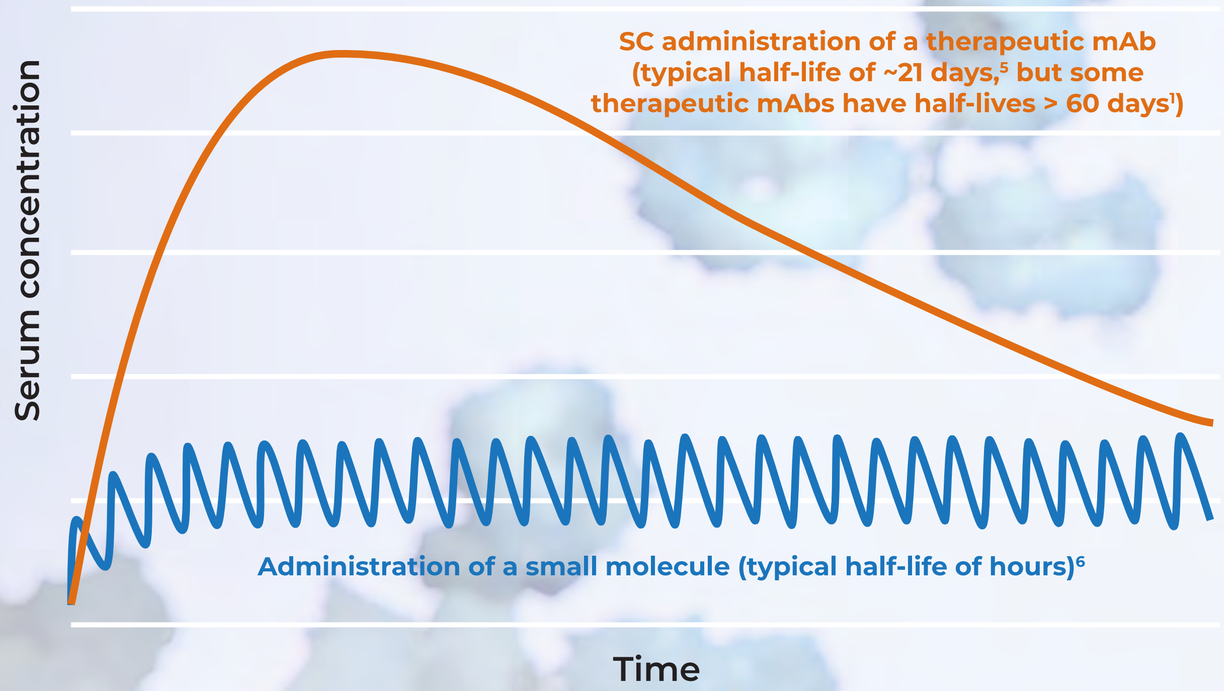
Therapeutic mAbs Have a Long Half-life, Ranging From Weeks to Months[1]

Simulated PK profiles for a therapeutic mAb (monthly SC) and a small-molecule drug (daily oral)[2-4,*]



Therapeutic mAbs have a long half-life, which may allow for longer dosing intervals[2,7]

mAb, monoclonal antibody; PK, pharmacokinetic; SC, subcutaneous.
*Small-molecule steady-state graphic depicts one-compartment serum concentrations. Figure is for illustrative purposes only. Simulation based on PK concepts in:

1. Robbie GJ, et al. *Antimicrob Agents Chemother*. 2013;6147-6153. **2.** Silberstein S, et al. *Headache*. 2015;55:1171-1182. **3.** Dhillon S and Kostrzewski A, eds. *Clinical Pharmacokinetics*. 2006:13-18. **4.** Crommelin DJA, et al, eds. *Pharmaceutical Biotechnology: Fundamentals and Applications*. 4th edition. 2013:157-164. **5.** Foltz IN, et al. *Circulation*. 2013;127:2222-2230. **6.** Gerber DE. *Am Fam Physician*. 2008;77:311-319. **7.** Carter PJ. *Nat Rev Immunol*. 2006;6:343-357.

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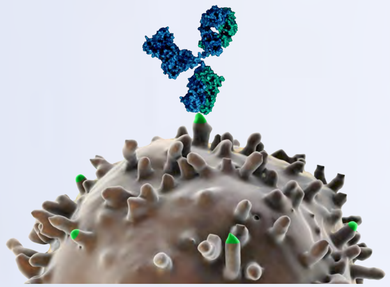
There Are Two General Classes of Toxicities That May Be Associated With Therapeutic mAbs

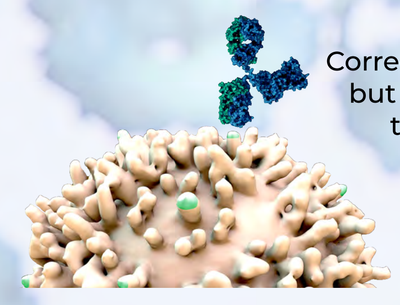
Target-related (on-target) toxicities

Intended tissue



Intended cellular effects and possible toxicity

Unintended tissue

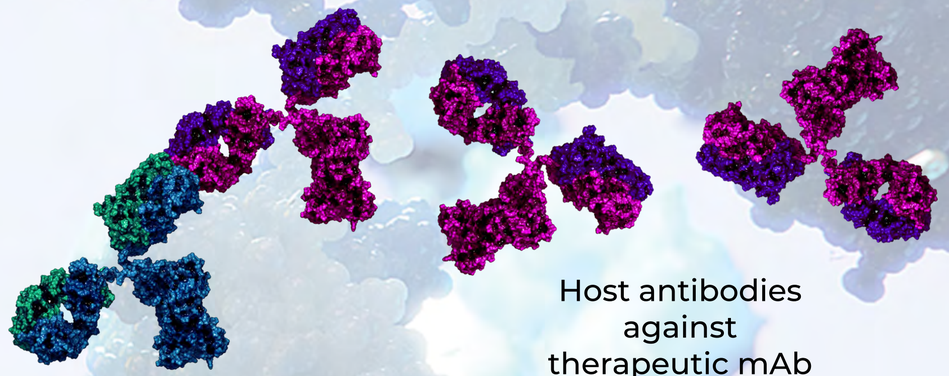


Unintended cellular effects (toxicity)

Therapeutic mAb target can influence the type of target-related adverse events that may occur

Non-specific (off-target) toxicities

Anti-antibody formation (immunogenicity)



Immunogenicity is independent of mAb target and an inherent risk with therapeutic mAbs

mAb, monoclonal antibody.

Foltz IN, et al. *Circulation*. 2013;127:2222-2230.

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Therapeutic mAbs Have a Low Potential for Drug-Drug Interactions (DDIs) When Coadministered With Small-Molecule Drugs[1]

Therapeutic mAbs and small molecules are unlikely to have DDIs when coadministered because they have different mechanisms of absorption, distribution, metabolism, and elimination[1,2]

Pathway affected	Potential for DDI when coadministered with another small molecule?*	
	Small-molecule drug[2]	Therapeutic mAb[1,3]
Absorption	+++	+/-
Distribution	+++	+/-
Metabolism	+++	+/-
Elimination	+++	+/-

+++ Likely +/- Unlikely

Please click below to learn more about the metabolism of

Small-molecule drugs

Therapeutic mAbs

DDI, drug-drug interaction; mAb, monoclonal antibody.
*Magnitude of DDI may vary based on pathway.
1. Serra López-Matencio JM, et al. *J Immunol Sci*. 2018;2:4-7. **2.** Roberts AG, et al. *Clin Pharmacol*. 2018;10:123-134. **3.** Hendrikx JJMA, et al. *Oncologist*. 2017;22:1212-1221.

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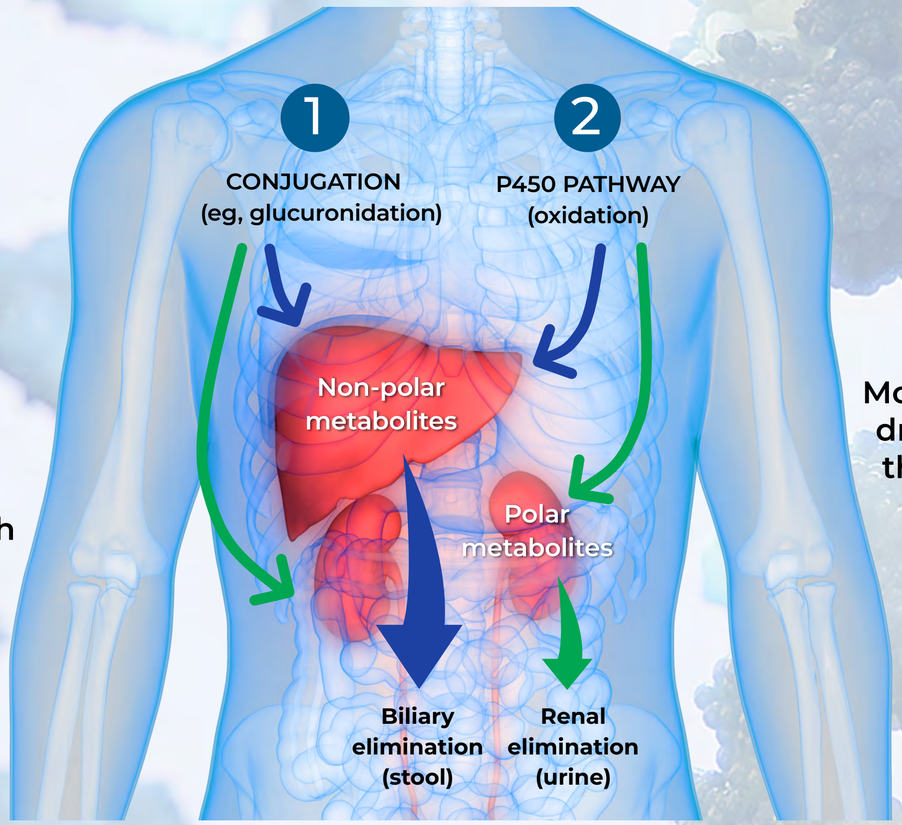
Small-molecule metabolism[1,2]

There are two major pathways of small-molecule metabolism[3]



Most of the remaining excretion occurs through the liver via bile[3]

More than two thirds of drug excretion occurs through the kidneys[3]

- Small molecules are generally metabolized and eliminated through hepatic/biliary or renal mechanisms[1]
- Many small molecules are metabolized by cytochrome P450 enzymes into chemical entities[2]

mAb, monoclonal antibody.

1. Foltz IN, et al. *Circulation*. 2013;127:2222-2230. **2.** Ogu CC, et al. *Proc (Bayl Univ Med Cent)*. 2000;13:421-423. **3.** Roberts AG, et al. *Clin Pharmacol*. 2018;10:123-134.

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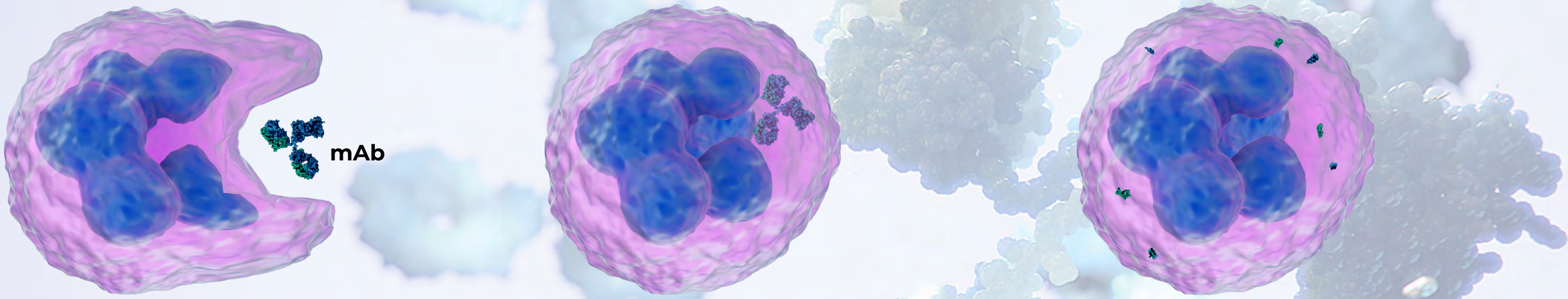
Therapeutic mAb metabolism[1-3]



- Antigen-bound or freely circulating, unbound therapeutic mAbs are broken down into amino acids or peptides by phagocytes in the **reticuloendothelial system**
- Therapeutic mAbs bound to membrane-bound antigen are internalized and broken down by the target cell in **target-mediated elimination**

mAb, monoclonal antibody.

1. Foltz IN, et al. *Circulation*. 2013;127:2222-2230. **2.** Silberstein S, et al. *Headache*. 2015;55:1171-1182. **3.** Tabrizi MA, et al. *Drug Discov Today*. 2006;11:81-88.

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Therapeutic mAbs Do Not Readily Cross the Intact Blood-Brain Barrier and Thus Have Minimal Distribution in the CNS[1]

Small-molecule drugs are typically found in organs, tissues, and plasma[2]

Because some small molecules can cross the blood-brain barrier, they may have a therapeutic effect on the CNS and/or may cause CNS-related toxicity[3,4]

Therapeutic mAbs are largely confined to the vasculature but may access target tissues through extravasation via convective transport[1,5]

Because the large size of therapeutic mAbs is likely to prevent them from crossing the intact blood-brain barrier, mAbs might not have a therapeutic effect on the CNS and are typically not associated with CNS-related toxicity[3,4,6,7]

Therapeutic mAbs may be > 100 times larger than small-molecule drugs[8] and therefore have different distributions throughout the body[1]

CNS, central nervous system; mAb, monoclonal antibody.

1. Foltz IN, et al. *Circulation*. 2013;127:2222-2230. **2.** Wan H. *ADMET DMPK*. 2016;4:1-22. **3.** Mikitsh JL, et al. *Perspect Medicin Chem*. 2014;6:11-24. **4.** Pardridge WM. *Mol Interv*. 2003;3:90-105. **5.** Silberstein S, et al. *Headache*. 2015;55:1171-1182. **6.** Lampson LA. *MAbs*. 2011;3:153-160. **7.** Gabathuler R. *Neurobiol Dis*. 2010;37:48-57. **8.** Zhao L, et al. *Acta Pharmacol Sin*. 2012;33:1339-1347.

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