Pharmacodynamics & Clinical Application of Therapeutics

Cancer Engineering

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Disclosures

- Lane Nguyen has no relevant financial or professional conflicts of interest to disclose.

Objectives

- Review pharmacodynamic principles and its relationship to the therapeutic effect
  - Receptor families
  - Signaling processes
- Identify administration factors influencing patient to patient variability in drug response
- Compare and contrast the various conventional methods for drug delivery
  - Ongoing challenges within in class
  - Developments with advanced drug delivery technology



Image: Thomas Eakins – *The Agnew Clinic*. 1889. Philadelphia Museum of Art.

Pharmacodynamics

- Relationship between drug concentration at the site of action and the resulting effect
  - Time course
  - Therapeutic intensity
  - Adverse effects

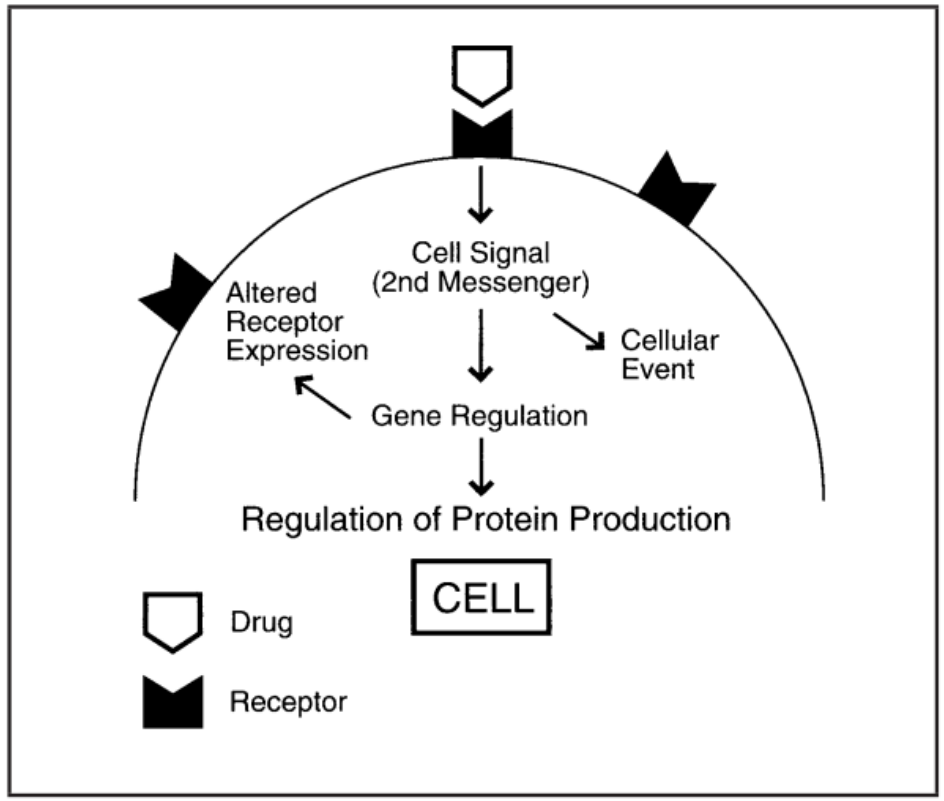


Image source: DiPiro's Pharmacotherapy: A Pathophysiologic Approach

Pharmacodynamics

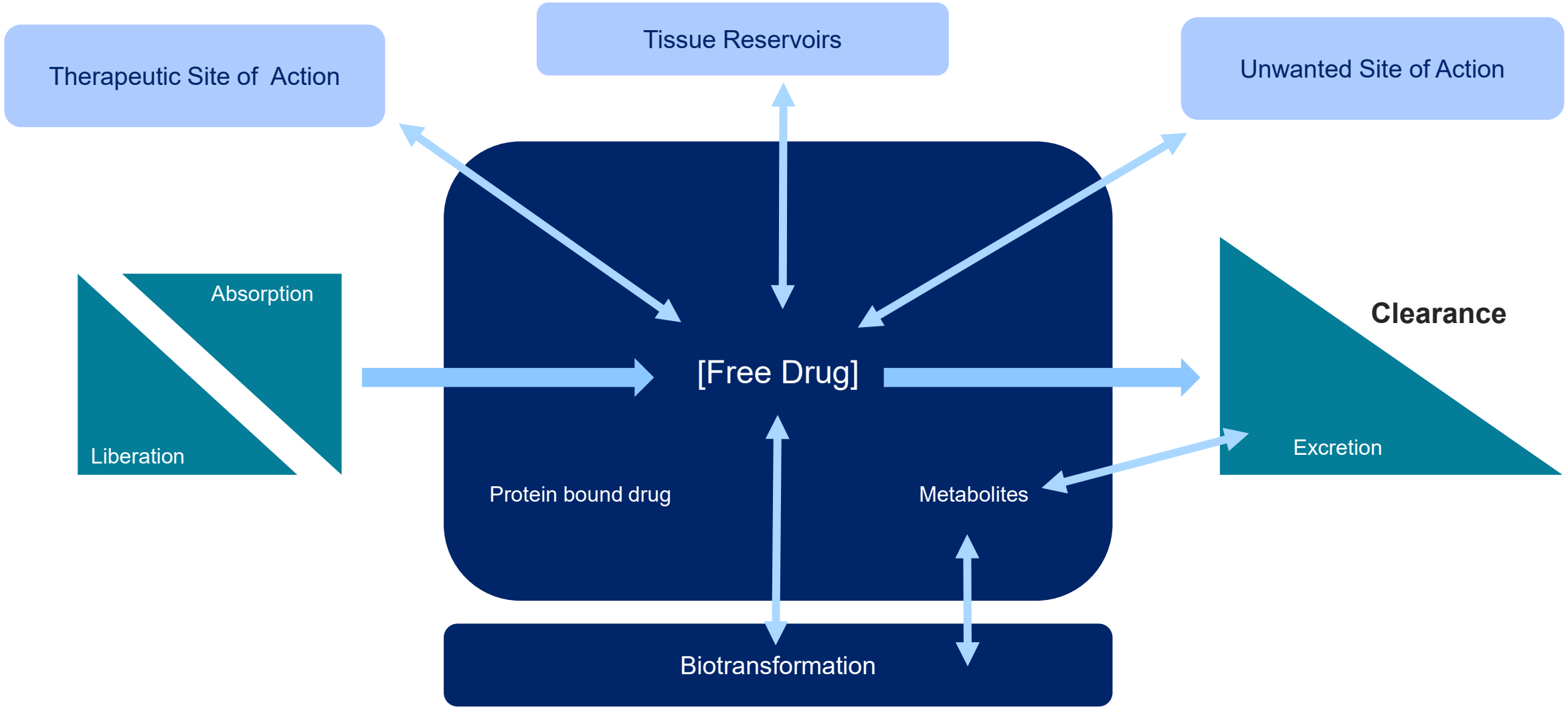
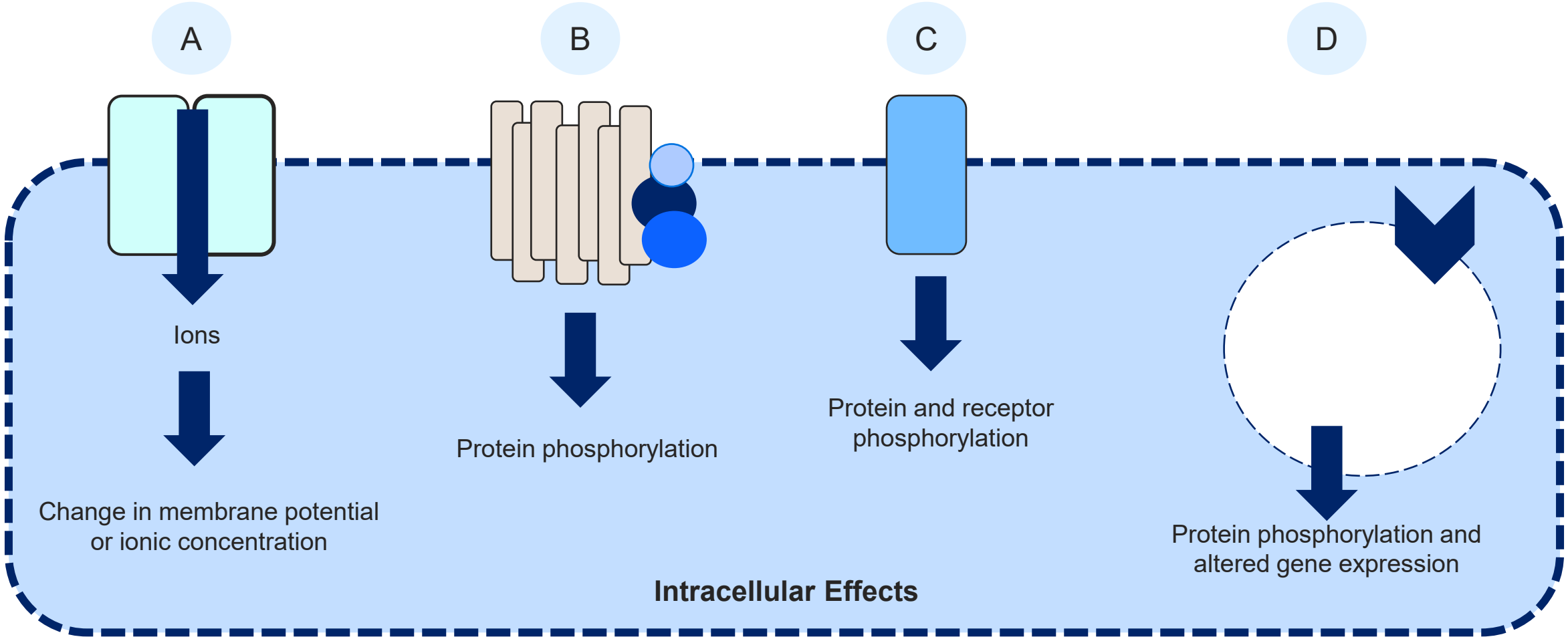


Image source adapted from: Goodman & Gilman's. The Pharmacological Basis of Therapeutics

Receptor Families

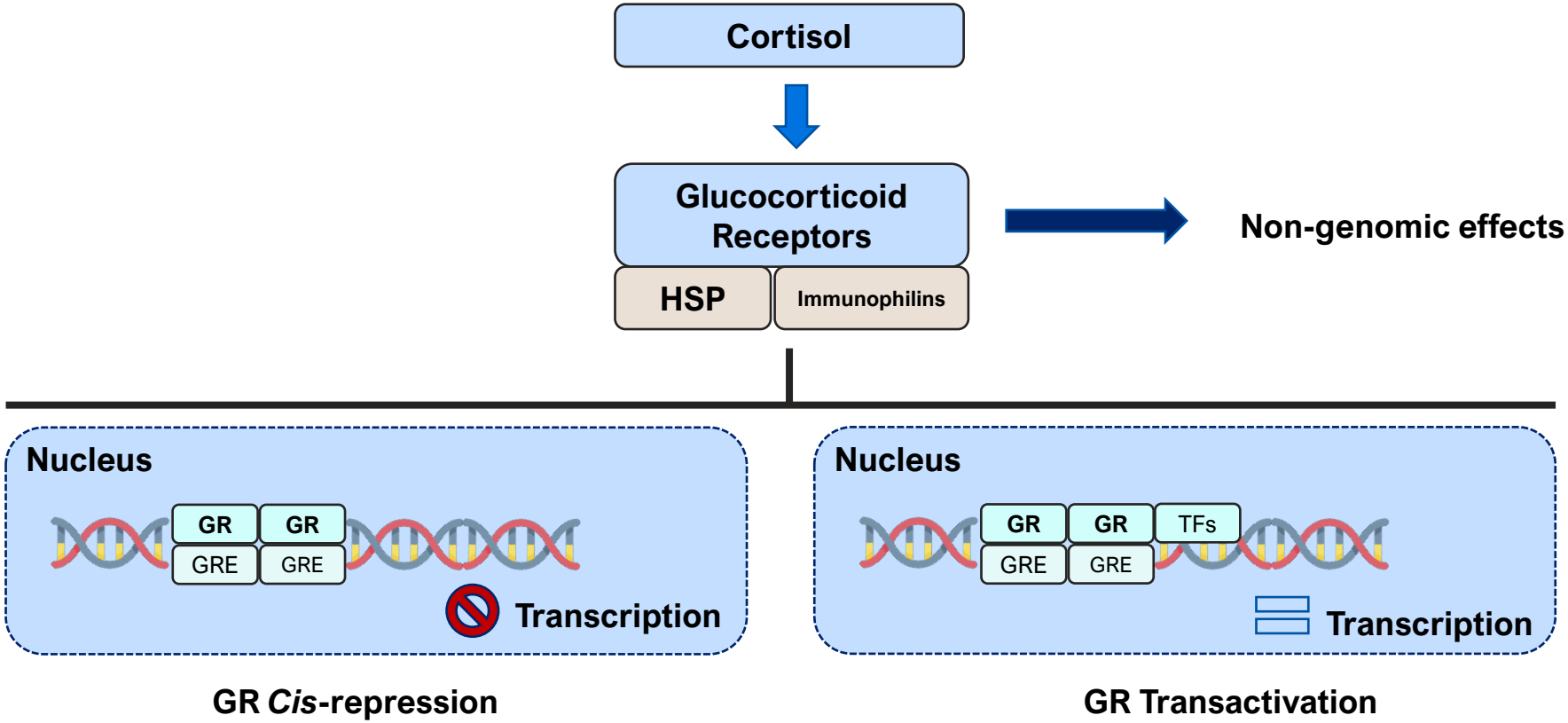


A. Ligand-gated Ion channels B. G protein-coupled receptors C. Enzyme-linked receptors D. Intracellular receptors.

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Corticosteroid Signaling

- Excessive cortisol activation associated with critical-illness induced corticosteroid insufficiency



HSP: Heat shock proteins, GR: Glucocorticoid receptor, GRE: Glucocorticoid response elements, TF: Transcription factors

Image adapted from: Annane D, Pastores S, et al. Intensive Care Med. 2017.

G-protein-coupled receptors (GPCR) Signaling

- β-adrenergic sympathomimetic activity in excess is deleterious for immune regulation

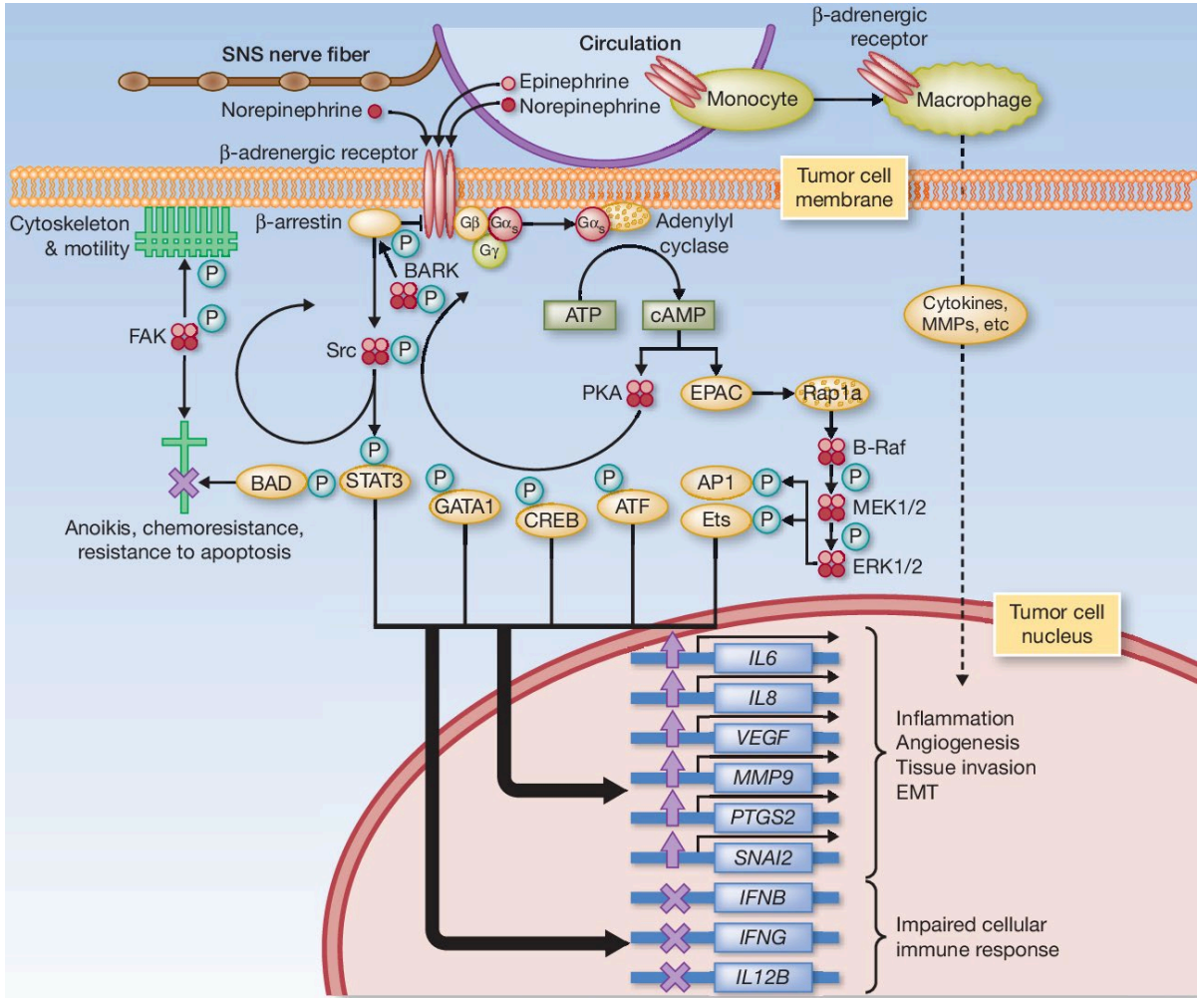
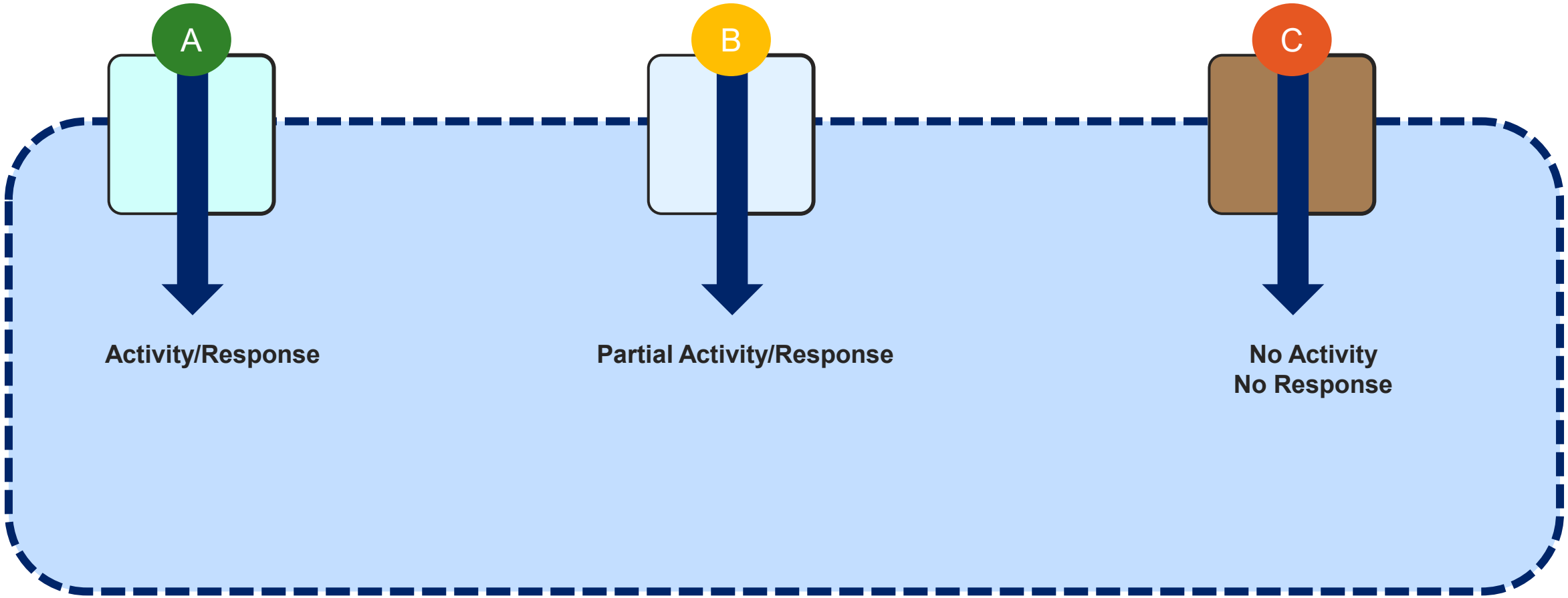


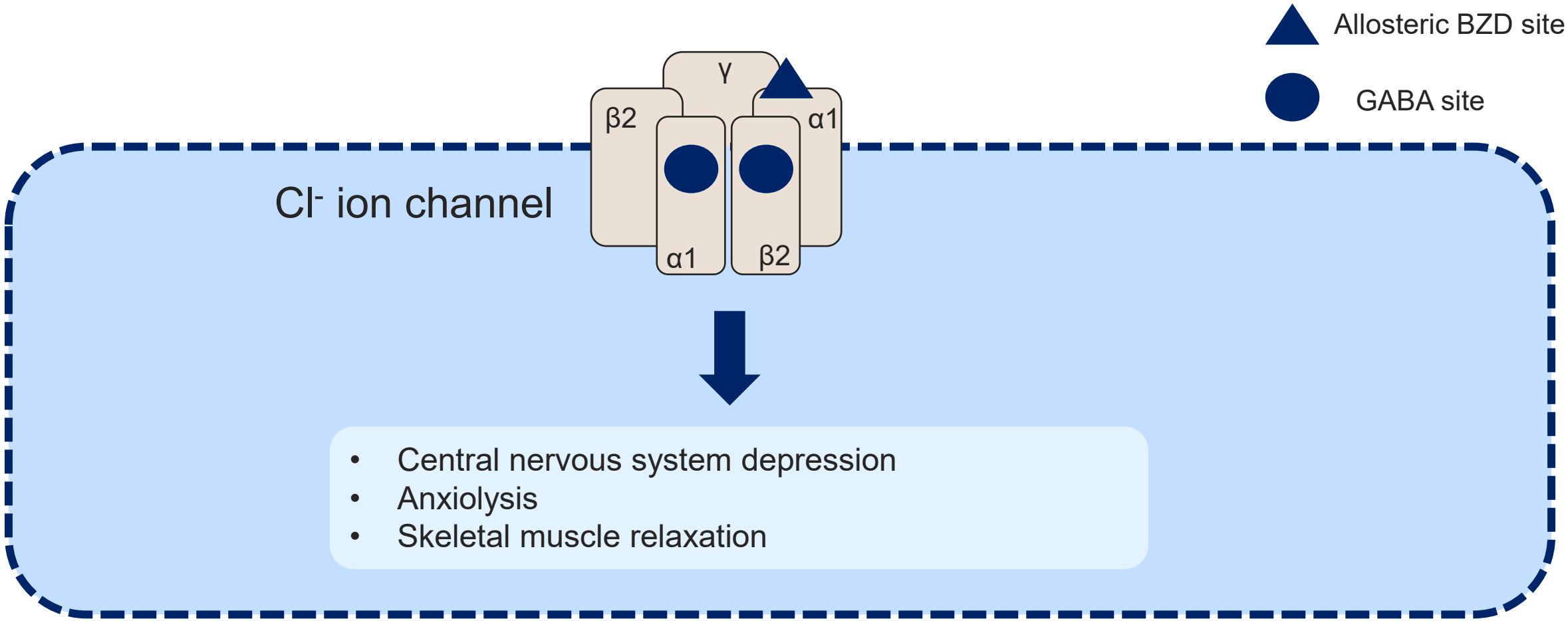
Image source from: Cole SW, et al. Clin Cancer Res. 2012.

Drug Action & Response



A. Agonist B. Partial Agonist C. Antagonist

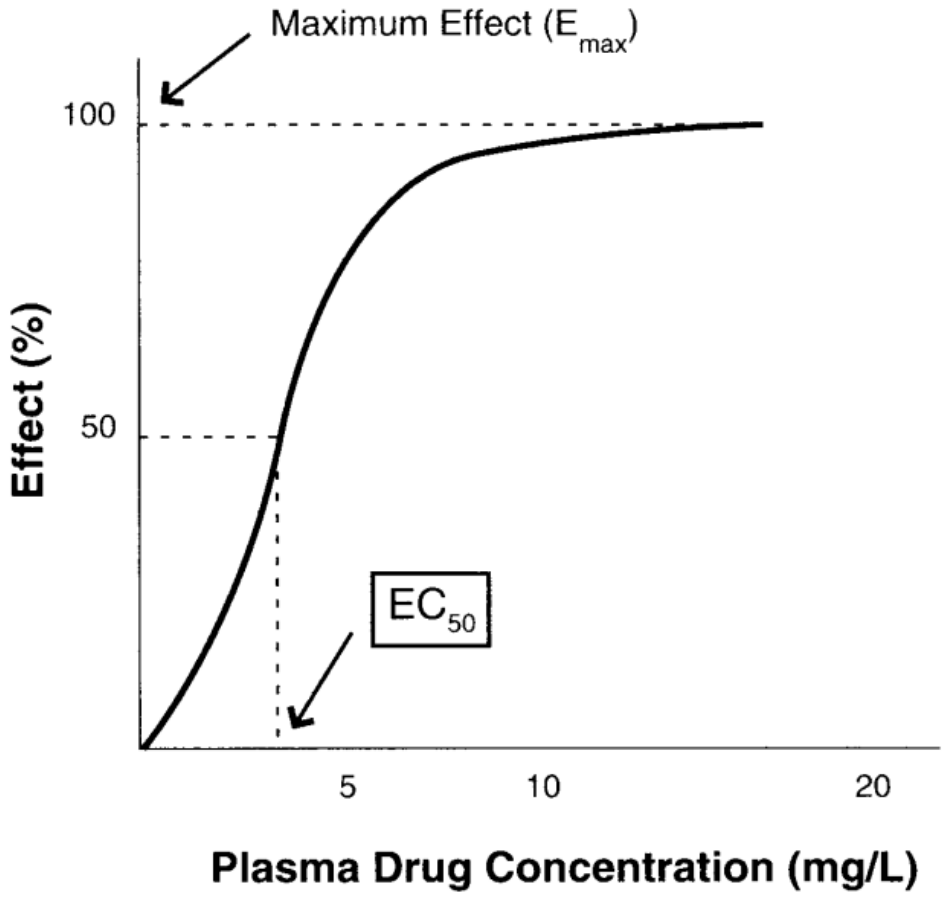
Allosteric Modulation



GABA: γ-amino butyric acid (major inhibitory neurotransmitter)

BZD: benzodiazepine

Consider the Logarithmic Scale on Effect



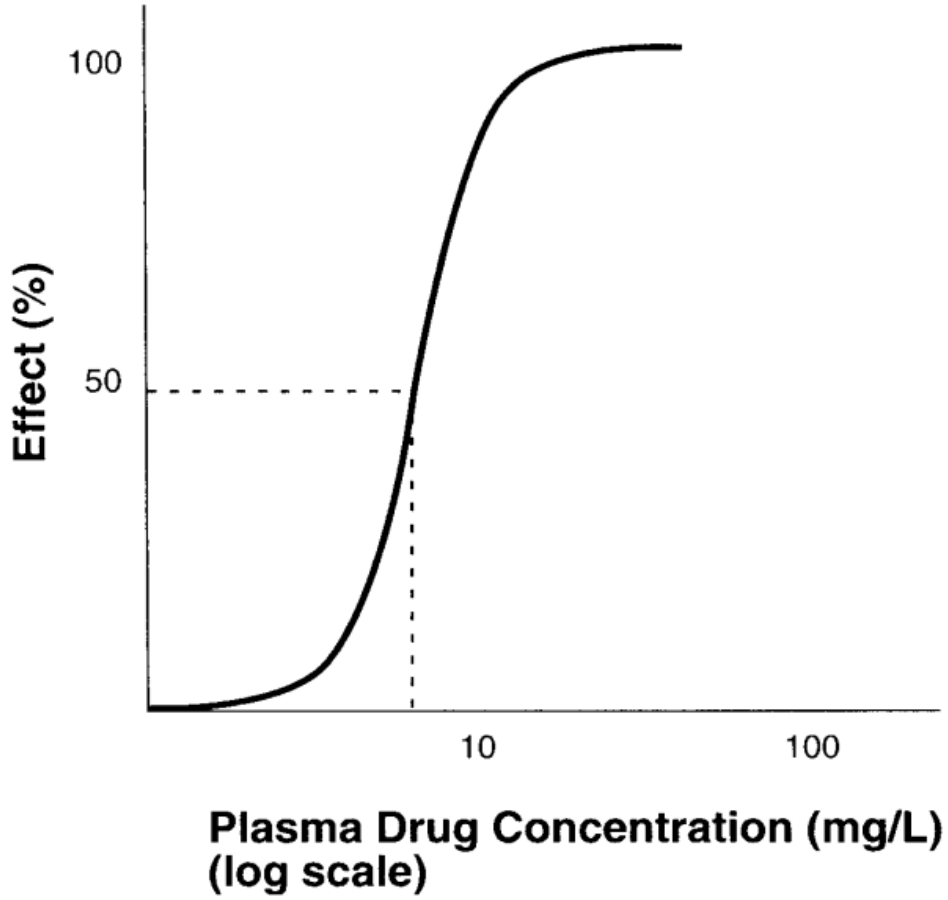


Image source: DiPiro's Pharmacotherapy: A Pathophysiologic Approach

Half Maximal Inhibitory Concentration – IC_{50}

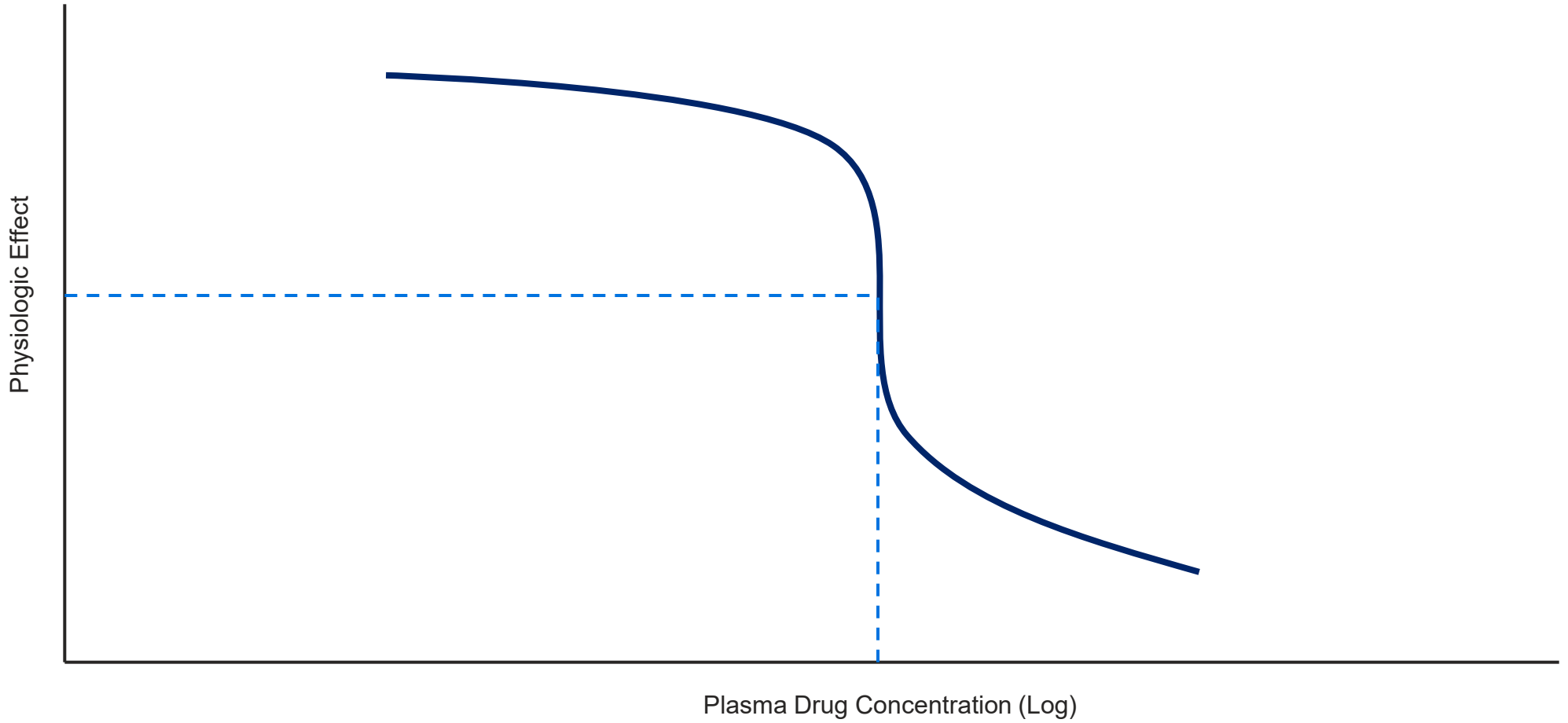


Image source adapted from: DiPiro's Pharmacotherapy: A Pathophysiologic Approach

A Discussion on Efficacy and Potency

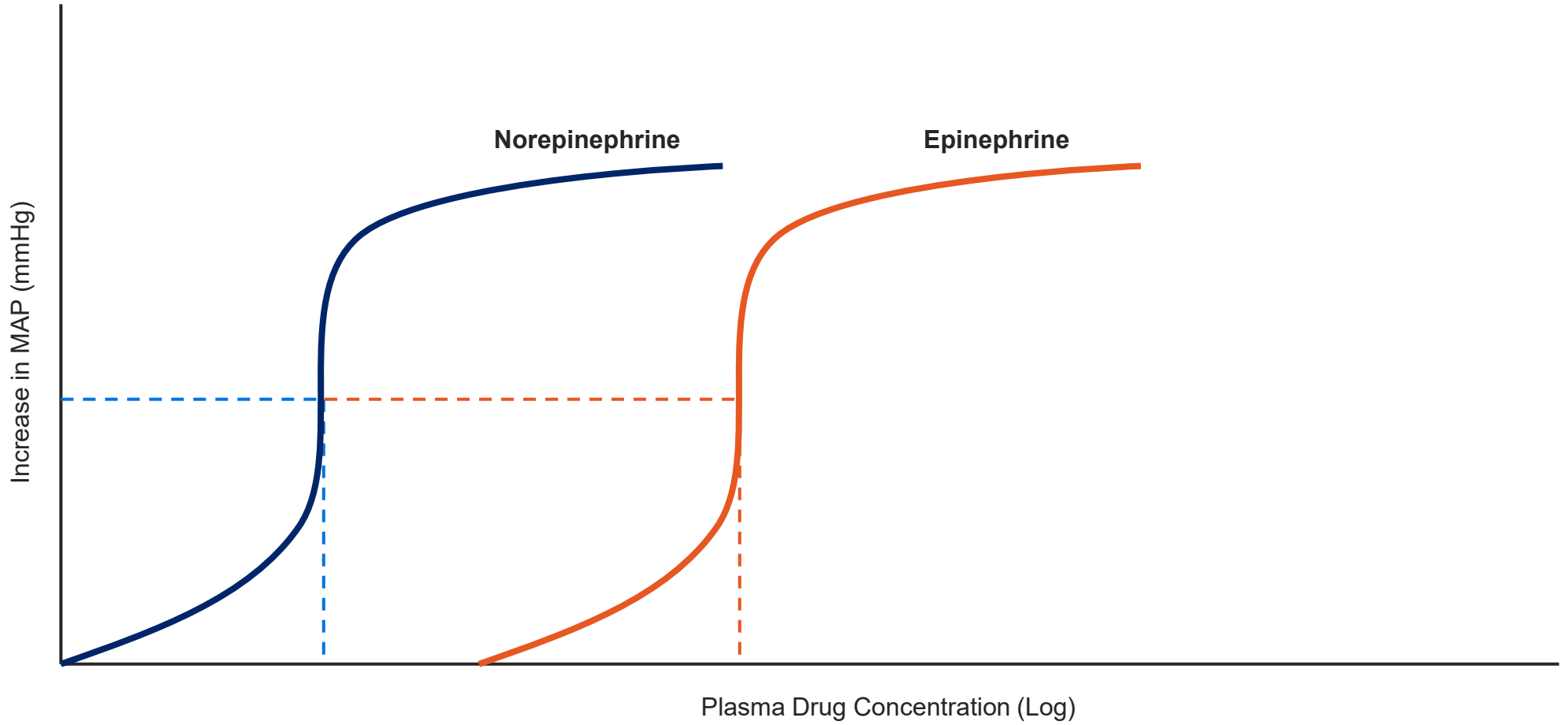


Image source adapted from: DiPiro's Pharmacotherapy: A Pathophysiologic Approach

Dose Response Curves

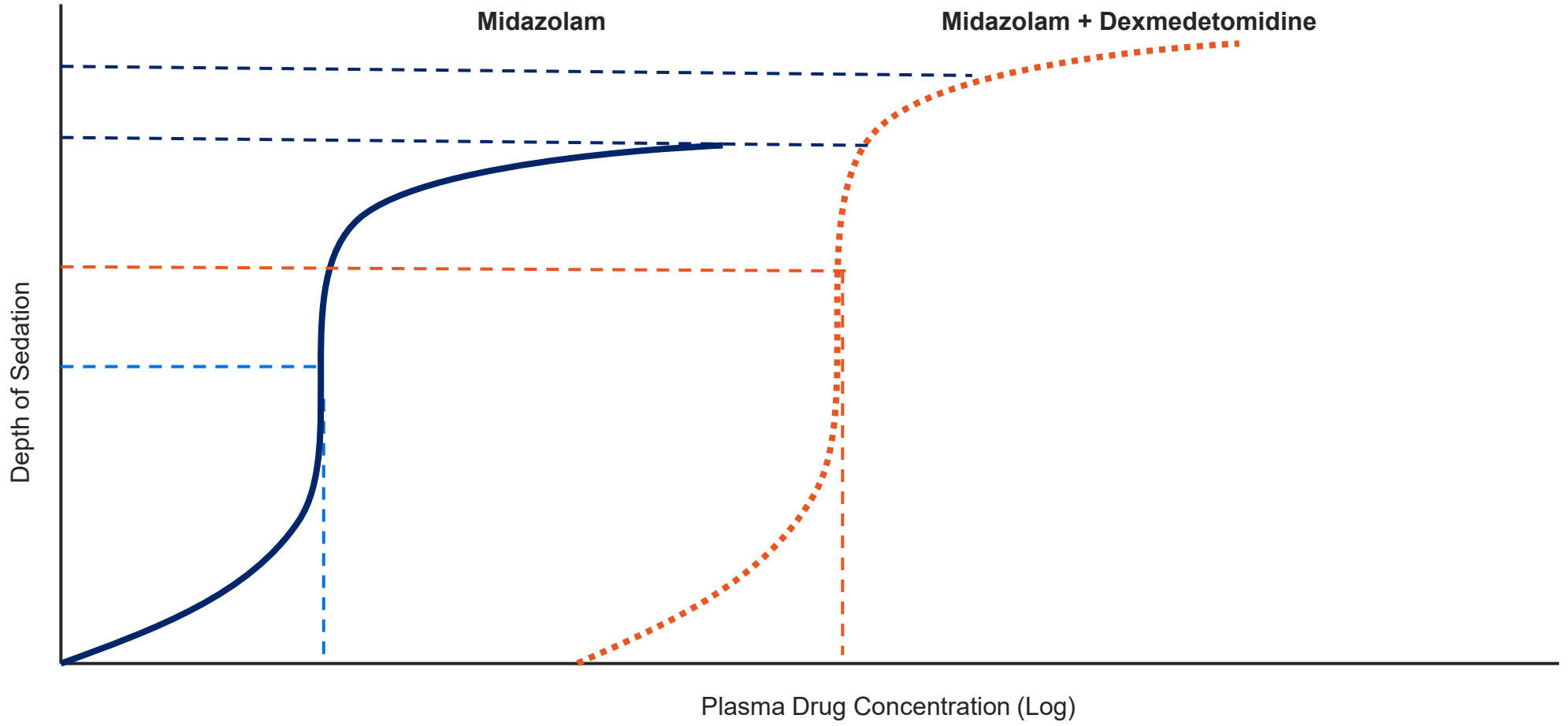


Image source adapted from: DiPiro's Pharmacotherapy: A Pathophysiologic Approach

Drug Tolerance

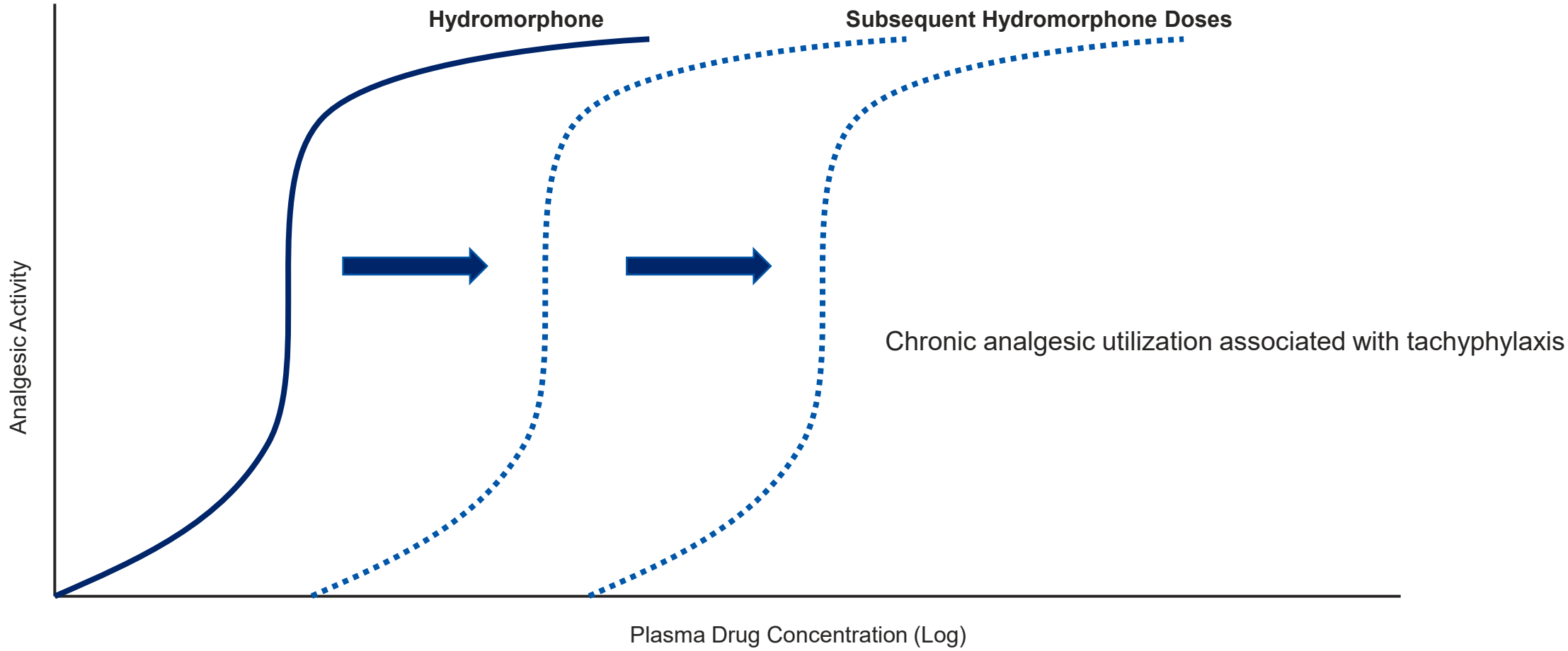


Image source adapted from: DiPiro's Pharmacotherapy: A Pathophysiologic Approach

Drug-drug Interactions

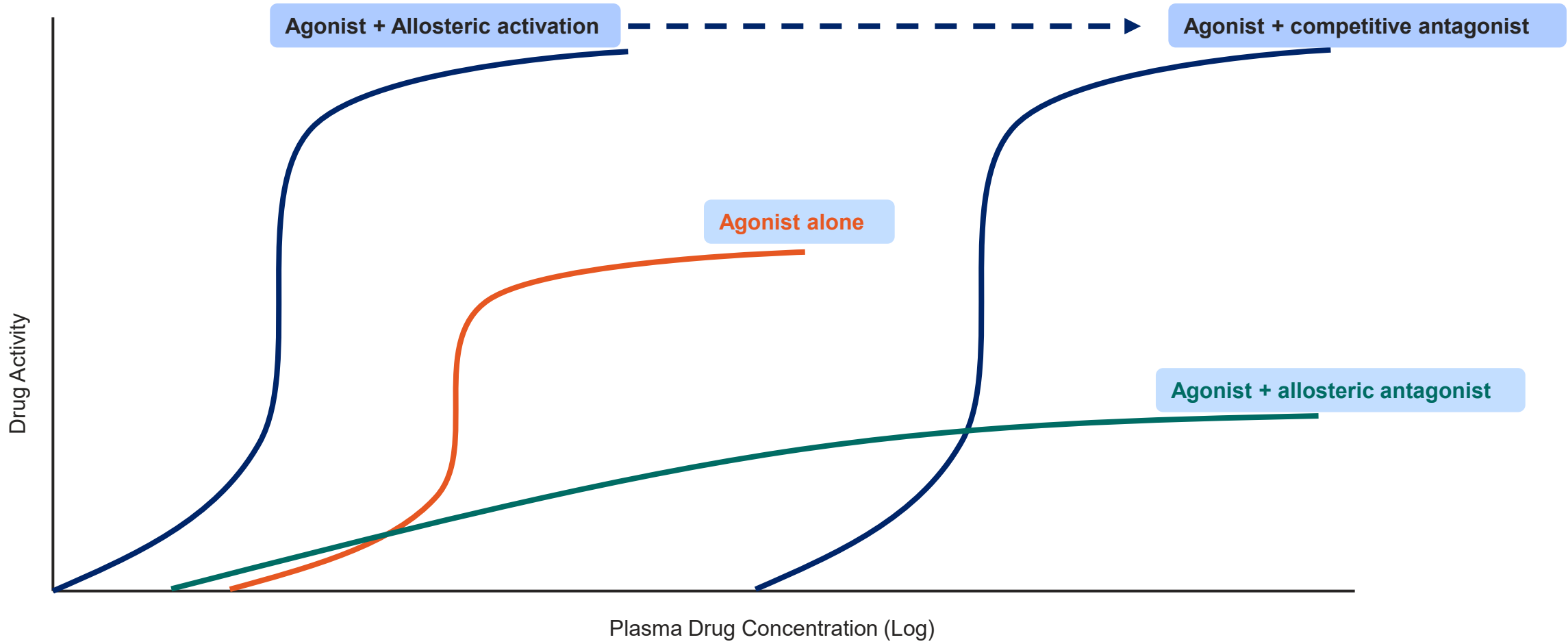


Image source adapted from: DiPiro's Pharmacotherapy: A Pathophysiologic Approach

Group Discussion

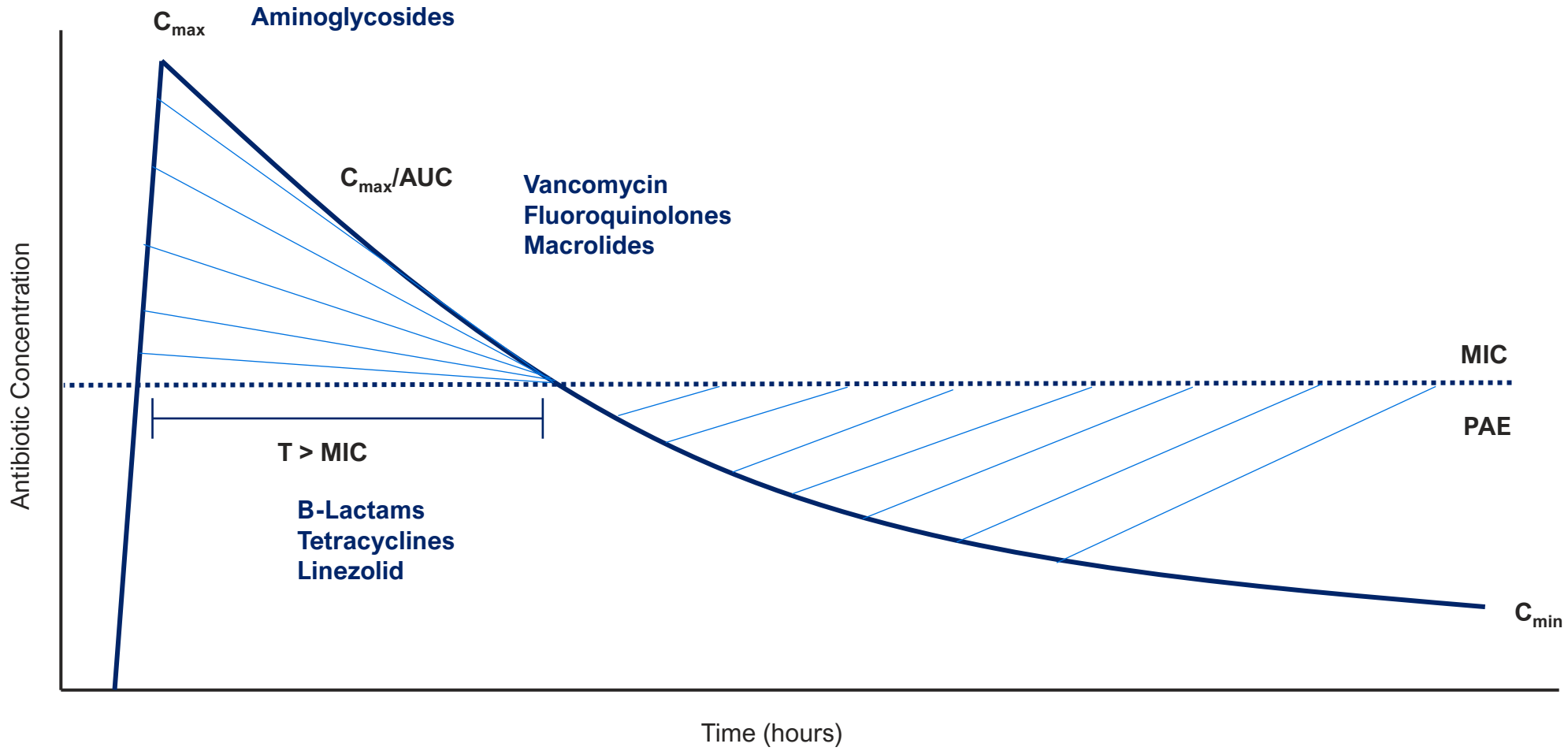
JT is 16-year-old male with recurrent **metastatic synovial sarcoma** s/p total laryngectomy admitted to the pediatric intensive care unit for **worsening dyspnea** and the need for continuous monitoring. He lost his airway during the otolaryngology evaluation at the bedside and experienced subsequent **cardiopulmonary arrest**.

Cardiopulmonary resuscitation was immediately performed and return of spontaneous circulation achieved after initial intervention. He remains **intubated**, **sedated**, and intermittently neuromuscular blocked.

Why would it be so difficult to optimize analgosedation in this patient?



The Pharmacodynamics of Antibiotics



MIC: Minimum inhibitory concentration; PAE: Post-antibiotic effect; AUC: Area Under the Curve

Image adapted from: Rybak MJ et al. *Am J Infect Control*. 2006

Balancing Efficacy and Toxicity

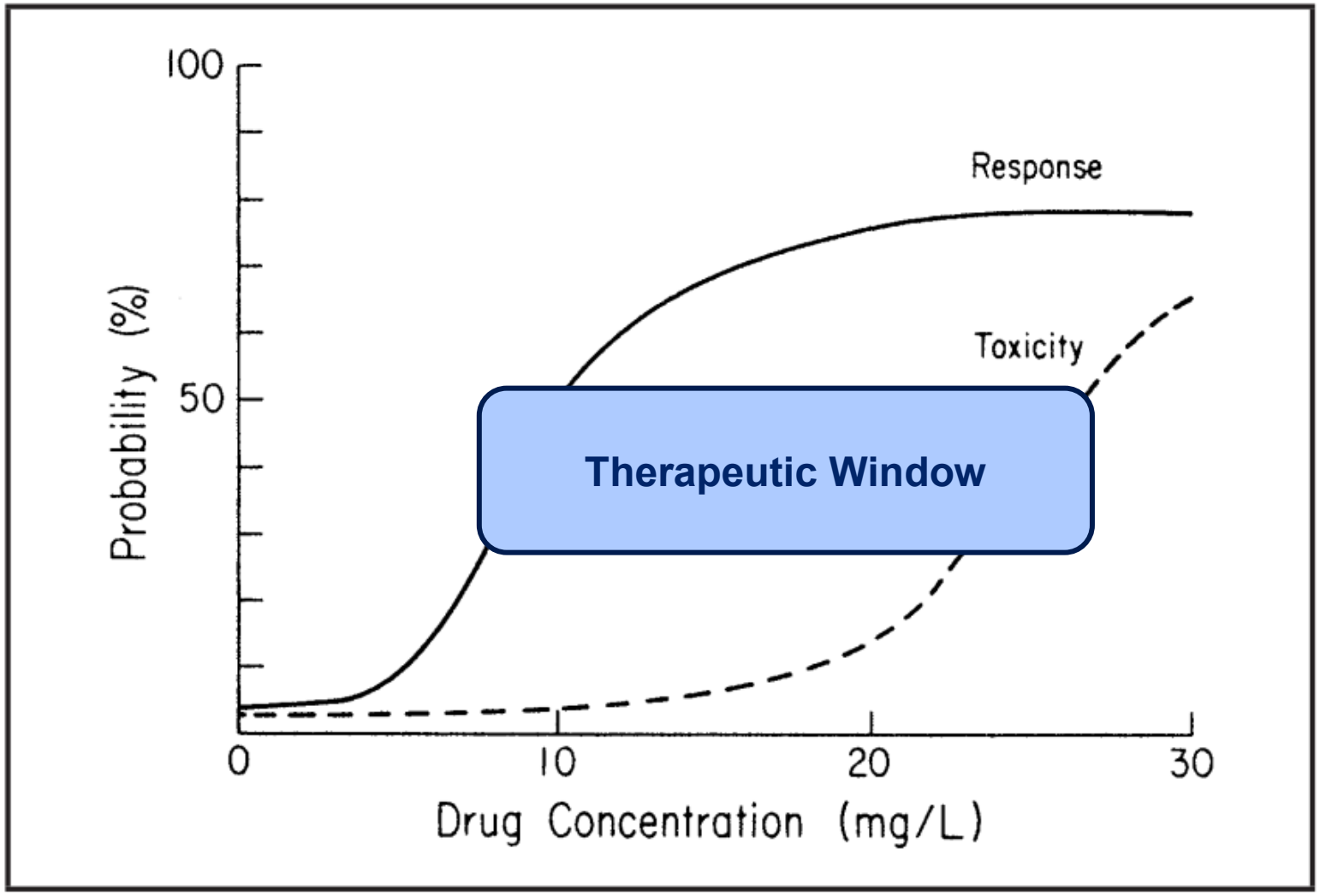


Image adapted from: Applied Pharmacokinetics. 1992.

Conventional Routes of Administration

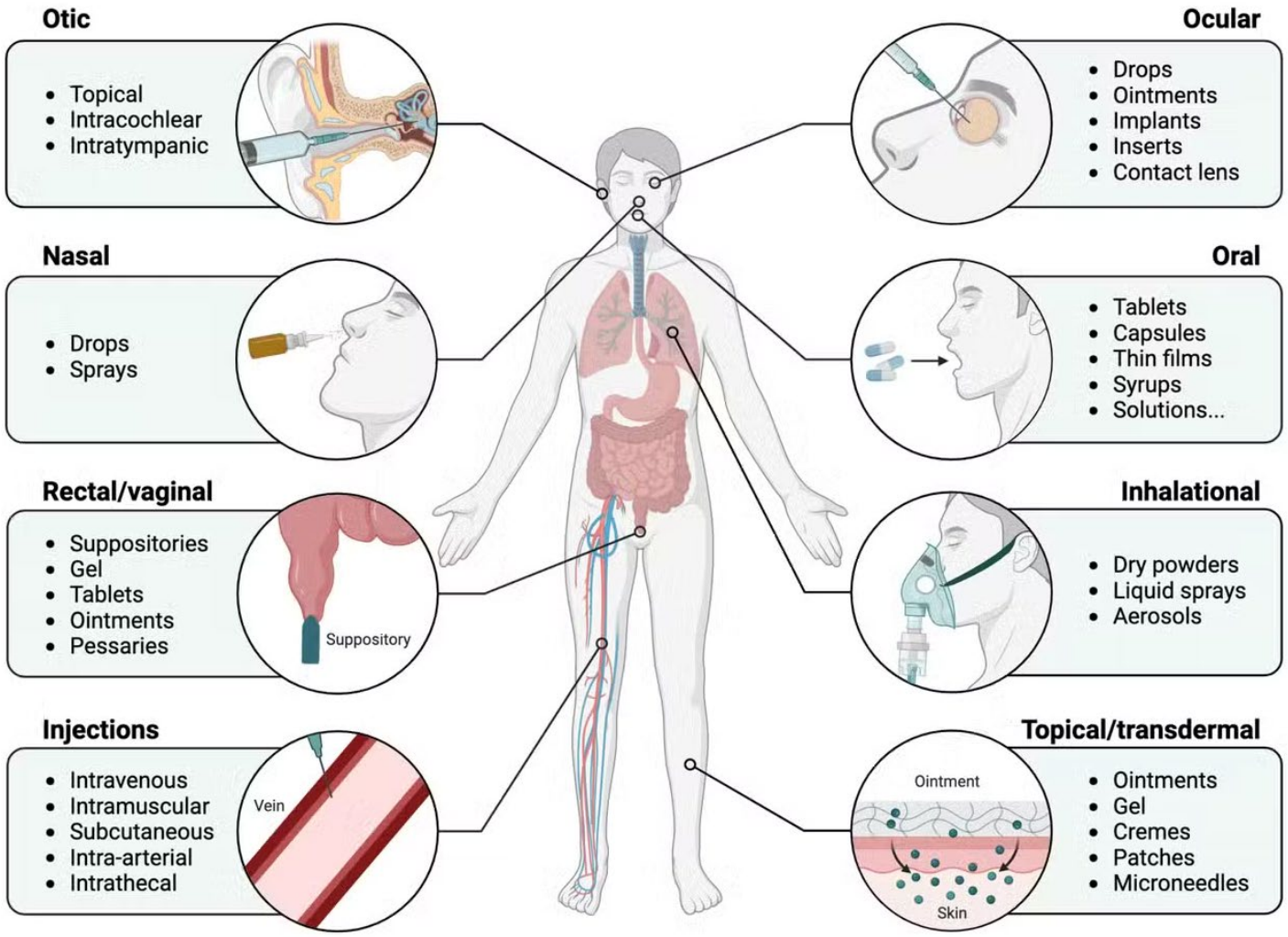


Image source: Sumathi Publications.

Physiological Alterations in Critical Illness

Variations in V_d

- Fluid balance
- Insensible losses
- Sensible losses

Changes in nonrenal clearance

- Hepatic dysfunction
- Acute respiratory distress
- Elevated intracranial pressures

Residual renal function

- Renal hypoperfusion
- Renal hyperperfusion



Drug-drug interference/interactions

- Competitive antagonism
- Allosteric modulation
- Inhibitors/Inducers

Blood pH

- Acidosis
- Alkalosis
- Mechanical ventilation

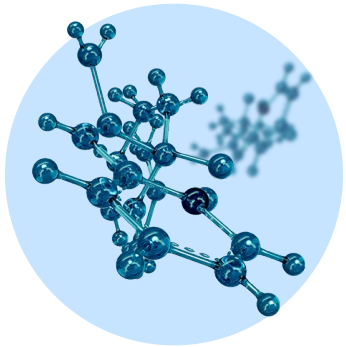
Hypoalbuminemia

- Burns
- Systemic capillary leak
- Malnutrition
- Post-operative complications

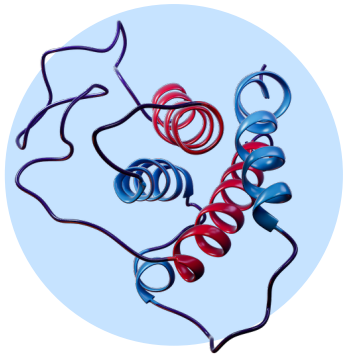
Wildschut ED, et al. *Intensive Care Med*. 2010.

Advances in Drug Delivery Systems

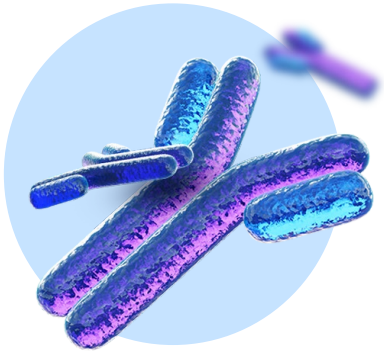
Small Molecules



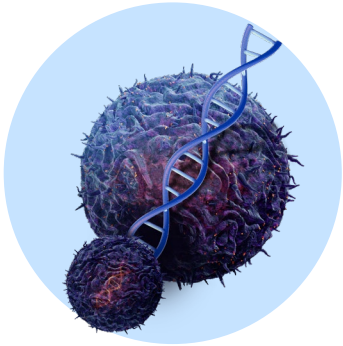
Proteins & peptides



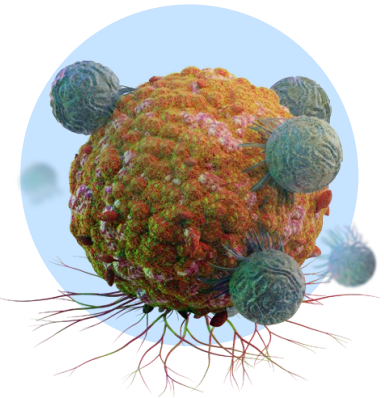
Antibodies



Nucleic Acids



Live Cells



Vargason, A.M. et al. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021

Image source: Bio-Techne, 2024.

Drug Delivery Systems

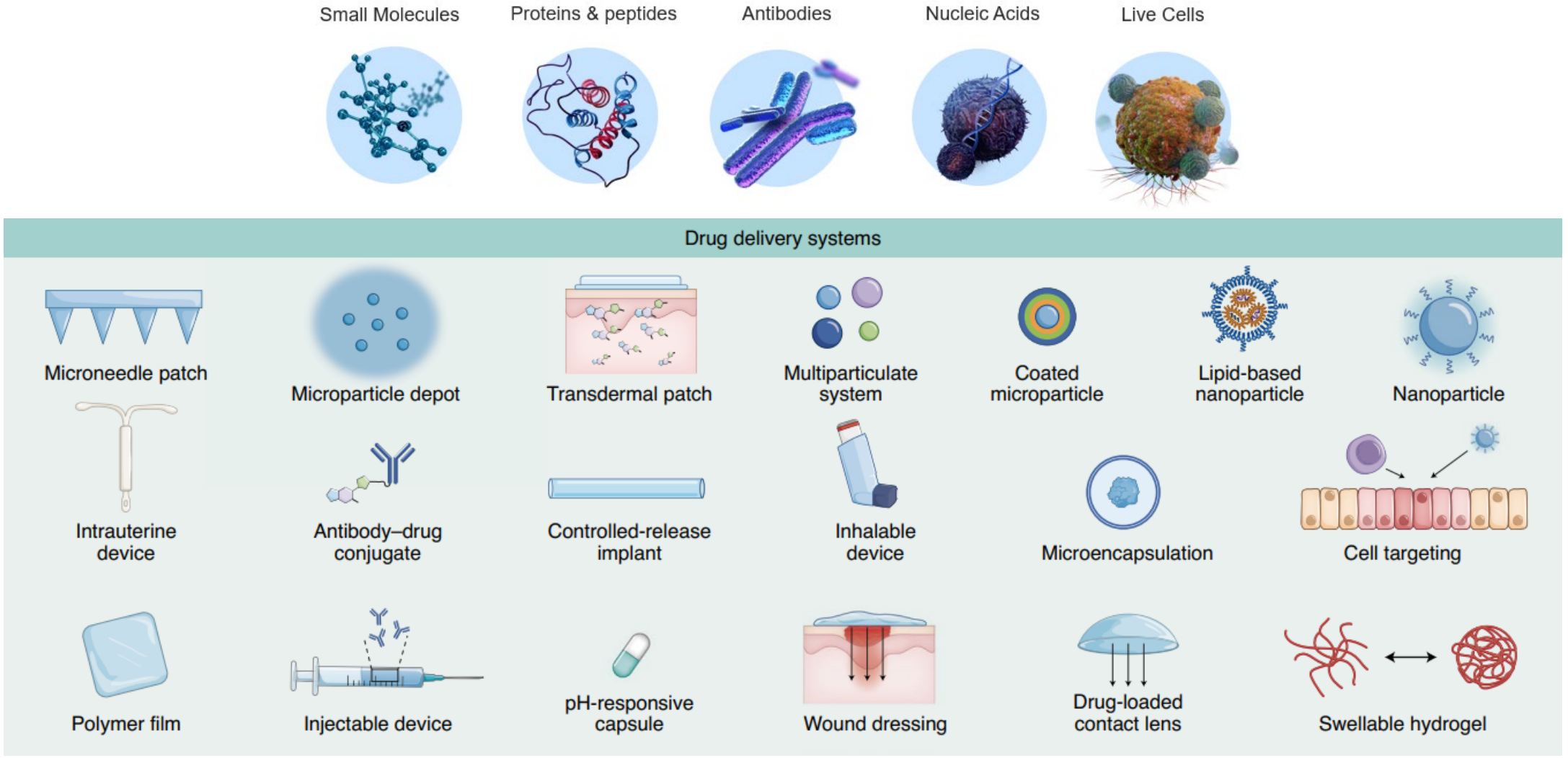


Image source: Vargason, A.M. et al. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021

Fentanyl Transdermal Application

- Fentanyl with highly potent analgosedative properties for time-controlled release in transdermal applications utilizes permeation enhancer with ethanol
- Significant safety concern for abuse or misuse

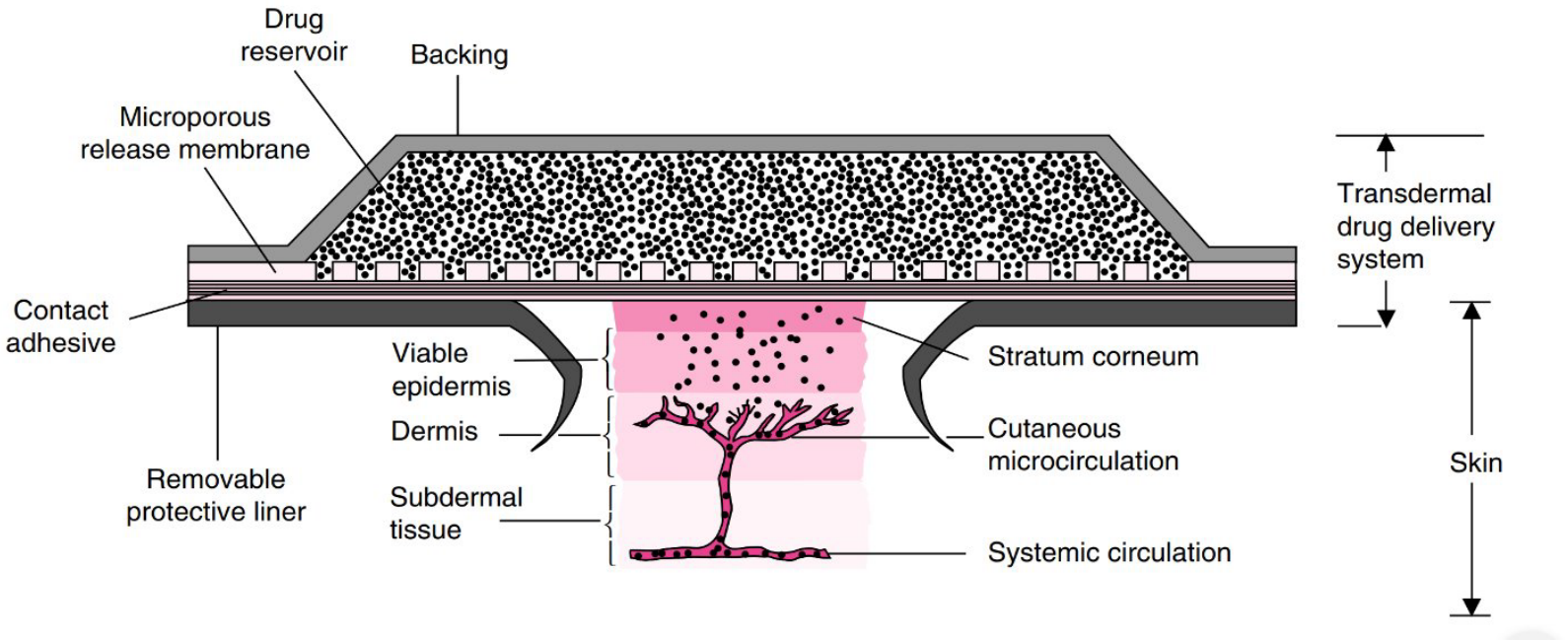


Image source: Muijsers RB et al. Drugs. 2001.

Advances in Drug Delivery Systems

Drug Modifications	Functional group modifications
	PEGylation
	Antibody humanization
	Amino acid substitutions
	Target-ligand conjugations
	Stimulation and differentiation
	Genetic engineering

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Advances in Drug Delivery Systems

Environmental Modifications	pH modification
	Permeation and enhancement
	Endosomal escape
	Dispersion enhancers
	Inhibition of drug clearance
	Normalization of the environment

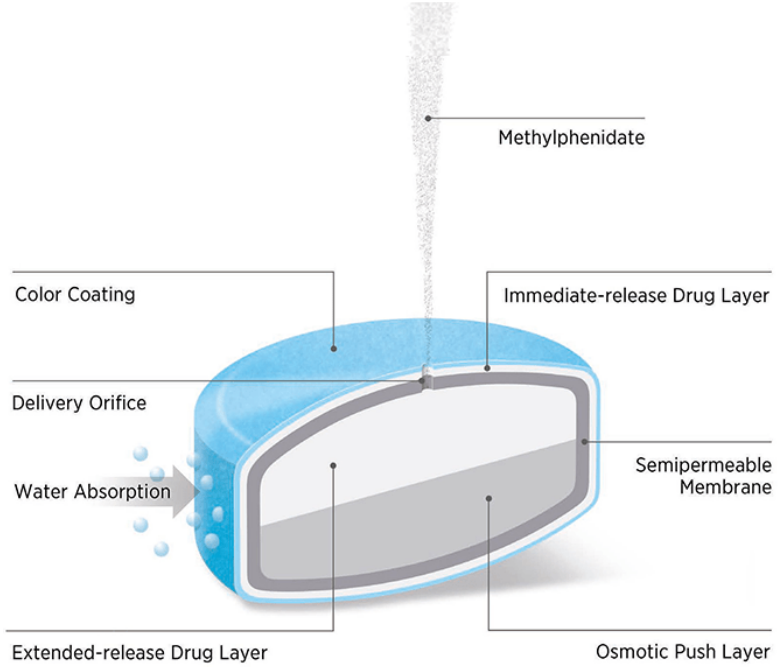
Challenges within Small Molecules

- **Controlling Pharmacokinetics**
  - Methylphenidate hydrochloride utilizes osmotic delivery system to improve pharmacokinetic release profile
- **Improving solubility**
  - Ritonavir, a modified thiazole, improves metabolic stability and aqueous solubility
- **Improving permeability to target site**
  - Benazepril contains alkyl ester prodrug moiety to mask ionizable groups to increase lipophilicity
- **Target development**
  - Ezetimibe is a selective cholesterol inhibitor discovered through library screening
- **Reducing off-target toxicity**
  - Naloxegol is pegylated naloxone used to prevent blood brain barrier permeability

Vargason, A.M. et al. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021

Challenges within Small Molecules

- **Controlling Pharmacokinetics**
  - Methylphenidate hydrochloride utilizes osmotic delivery system to improve pharmacokinetic release profile



Vargason, A.M. et al. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021

Image source: Vertical Pharmaceuticals. Relexxii (methylphenidate hydrochloride extended-release tablets)

Challenges within Proteins and Peptides

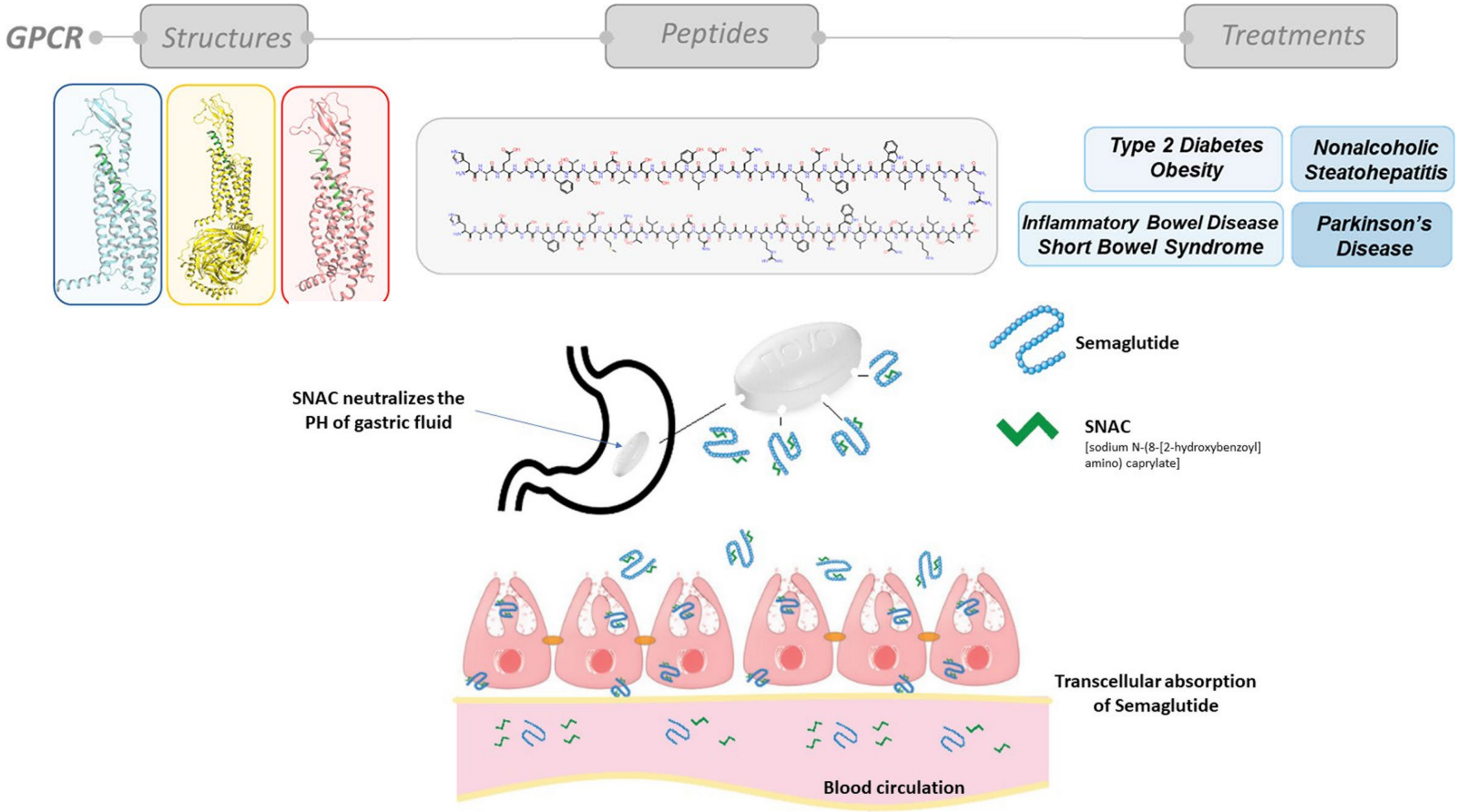
- **Controlling Pharmacokinetics**
  - Leuprolide acetate is a sustained microsphere formulation of luteinizing hormone-releasing hormone providing a stable release profile upon steady state concentrations
- **Improving physiochemical stability**
  - Desmopressin (DDAVP), the analogue to arginine vasopressin, contains a non-amino acid substitution for improving half-life and stability
- **Non-invasive administration**
  - Inhaled insulin products consists of microparticles with increased surface area for suitable delivery and absorption
- **Bypassing biological barriers**
  - Semaglutide formulated with sodium N-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC) for oral absorption
- **Reducing immunogenicity**
  - Pegademase bovine is a PEGylated protein with extended half-life and reduced immunogenicity
- **Improving target selectivity**
  - Beletacept is a fusion protein with amino acid substitutions for improved selectivity to CD86 and CD80

Vargason, A.M. et al. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021

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The Changing Landscape of Obesity Treatments

- **Bypassing biological barriers**
  - Semaglutide formulated with sodium N-(8-[2-hydroxybenzoyl]amino)caprylate (SNAC) for oral absorption



Suzuki, R. et al. Recent Developments in Therapeutic Peptides for GLP-1 and GLP-2 Receptors. J Med Chem. 2020.

Challenges within Antibodies

- **Controlling Pharmacokinetics**
  - Certolizumab pegol is the first FDA-approved PEGylated antibody fragment extending half-life and increases solubility
- **Improving stability**
  - Blinatumomab is a lyophilized antibody with trehalose for improved stability of the antibody structure
- **Non-invasive administration**
  - Trastuzumab and hyaluronidase-oysk is a subcutaneous depot with hyaluronidases for the sustained release of trastuzumab
- **Bypassing biological barriers**
- **Reducing immunogenicity**
  - Panitumumab, the first FDA-approved fully human antibody, reducing immunogenicity and preventing the generation of anti-antibodies
- **Achieving high doses**
  - Tocilizumab as a subcutaneous formulation with excipients allows high antibody concentration delivery

Vargason, A.M. et al. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021

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Challenges within Antibodies

- **Improving stability**
  - Blinatumomab is a lyophilized antibody with trehalose for improved stability of the antibody structure
    - In Pediatrics; used for first-line treatment in children receiving post remission intensive chemotherapy for ALL; administered as continuous infusion for 28 days
    - Infantile *KMT2A*-rearranged ALL; added after Interfant-06 induction chemotherapy

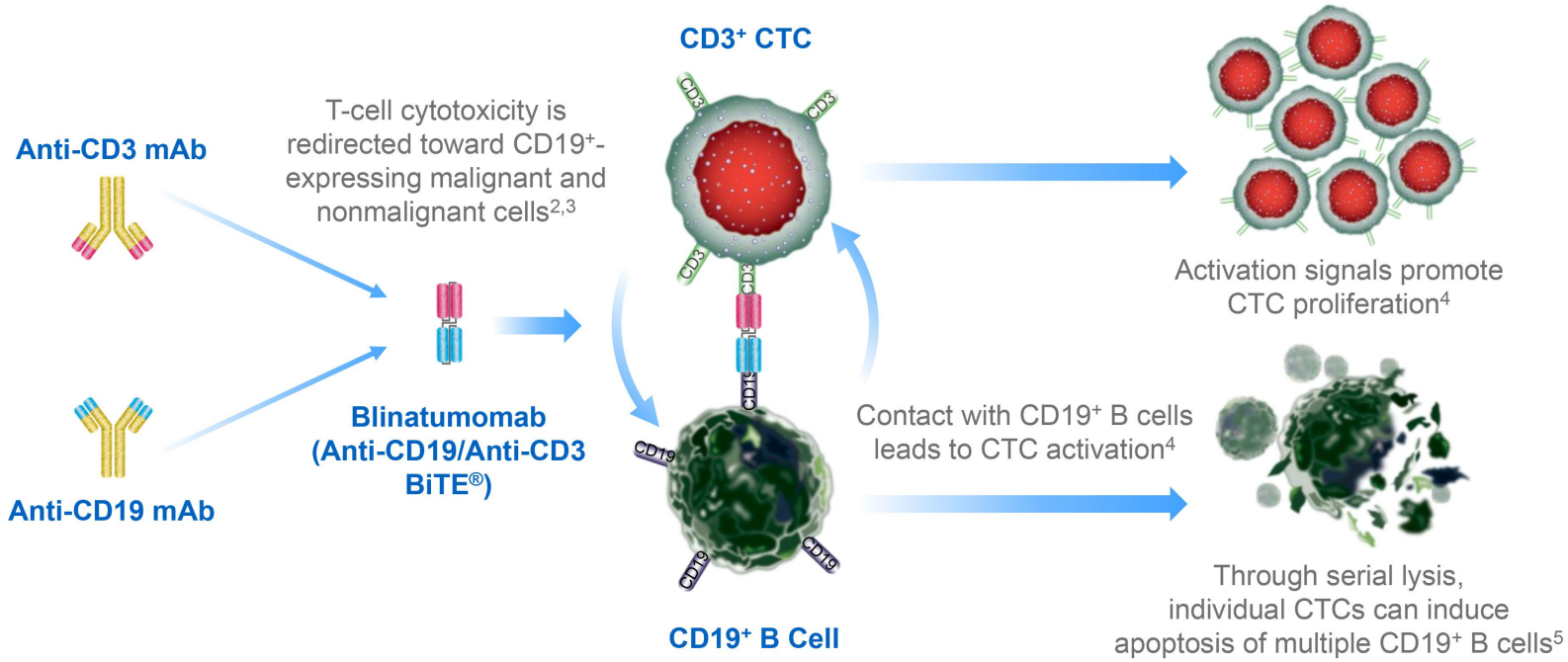
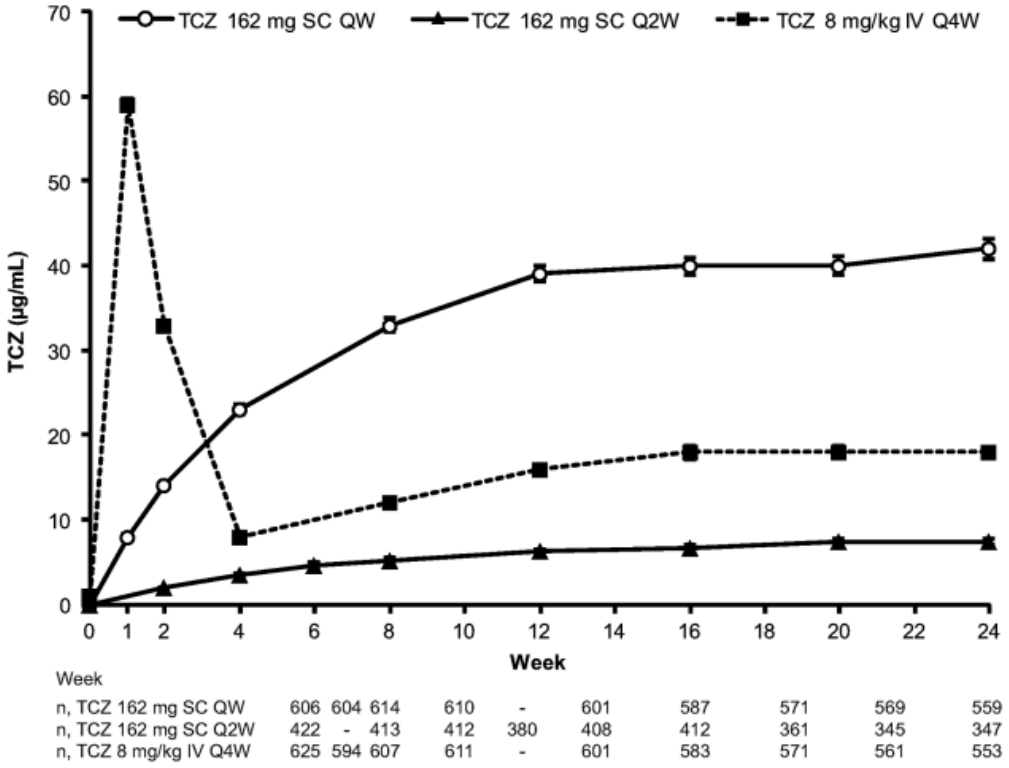


Image source: Locatelli F, et al. *Blood Cancer Journal*. 2020.

Vargason, AM, et al. The evolution of commercial drug delivery technologies. *Nat Biomed Eng*. 2021

Challenges within Antibodies

- **Achieving high doses**
  - Tocilizumab as a subcutaneous formulation with excipients allows high antibody concentration delivery



Week										
n, TCZ 162 mg SC QW	606	604	614	610	-	601	587	571	569	559
n, TCZ 162 mg SC Q2W	422	-	413	412	380	408	412	361	345	347
n, TCZ 8 mg/kg IV Q4W	625	594	607	611	-	601	583	571	561	553

Figure 1. Mean observed predose tocilizumab concentrations for SC QW, SC Q2W, or IV Q4W dosing. Error bars show standard error. IV, intravenous; Q2W, every 2 weeks; Q4W, every 4 weeks; QW, weekly; SC, subcutaneous; TCZ, tocilizumab.

Abdallah H. et al. *J Clin Pharmacol*. 2017.

Group Discussion

Even with achieving improved stability with blinatumomab therapy, what barriers or concerns do you have with prolonged continuous infusions for the patient?

What solutions could take place to improve patient safety and efficacy?

What are your thoughts on rapid delivery to achieve high drug exposure for this situation?



Challenges within Nucleic Acids

- **Controlling Pharmacokinetics**
  - Patisiran, first FDA-approved siRNA-based therapy, lipid nanoparticles improves trafficking to the liver and cellular uptake
- **Improving physiochemical stability**
  - Fomivirsen, first FDA-approved antisense oligonucleotide, incorporates a phophorothioate backbone modification for improved stability against nucleases
- **Bypassing the target cell membrane**
  - Givosiran, a GalNAc-SiRNA conjugate for improved hepatocellular uptake
- **Accessing intracellular machinery (e.g., cytosol or nucleus)**
  - Patisiran contains ionizable cationic lipids mediating endosomal escape following endocystosis
- **Reducing immunogenicity**
  - Nusinersen, first FDA-approved therapy for spinal muscular atrophy, contains 2'-O-methoxyethyl phosphorothioate modification to reduce immunogenicity and improves stability
- **Preventing off-target gene editing**
  - CRISPR-CCR5-modified $CD34^{+}$ cells for HIV-1

Vargason, A.M. et al. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021

Challenges within Nucleic Acids

- **Reducing immunogenicity**
  - Nusinersen, first FDA-approved therapy for spinal muscular atrophy, contains 2'-O-methoxyethyl phosphorothioate modification to reduce immunogenicity and improves stability

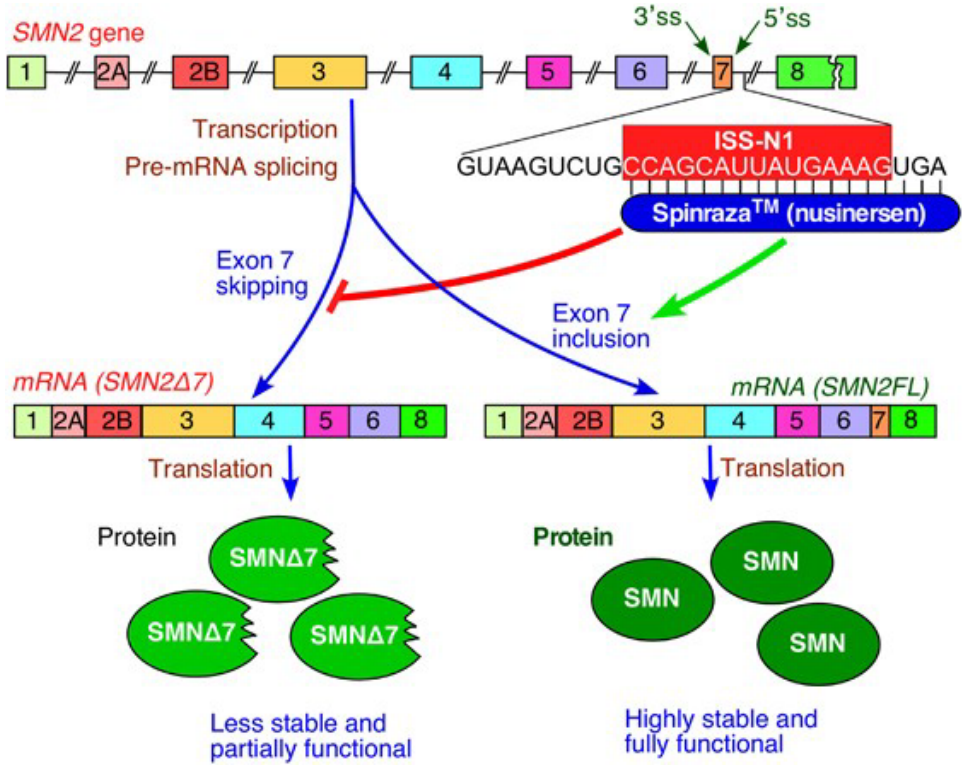


Image from: Singh NN, et al. *Gene Therapy*. 2017.

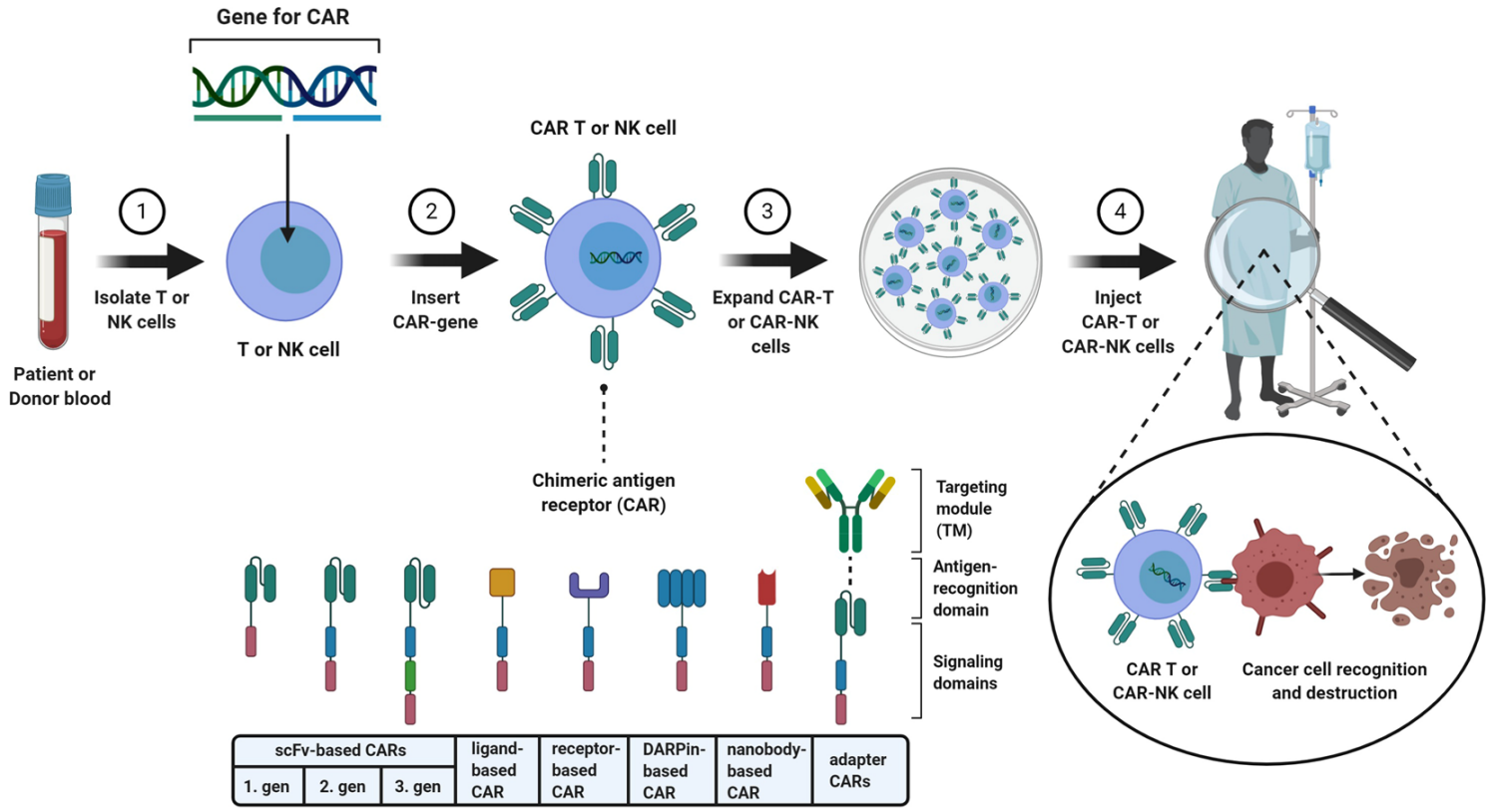
Challenges within Live Cells

- **Controlling unpredictable Pharmacokinetics**
  - Preclinical alginate-based biopolymer implants for the controlled release of CAR T cells directly at the site of action
- **In vivo persistency and viability**
  - SIG-001, factor-VIII-secreting genetically engineered cells in an antifibrotic matrix
- **Reducing immunogenicity**
  - Fludarabine conditioning chemotherapy for CAR T cells; conditioning regiment intensity reducing immune reactivity and rejection of the infused constructs
- **Maintaining therapeutic cell phenotype**
  - Sipuleucel-T, first FDA-approved cell-based (dendritic cell) immunotherapy induces and maintains therapeutic phenotype throughout ex vivo antigen presentation
- **Targeting to disease location**
  - Matrix-induced autologous chondrocyte implantation for the maintenance of chondrocytes at the site of action

Vargason, A.M. et al. The evolution of commercial drug delivery technologies. Nat Biomed Eng. 2021

Challenges within Live Cells

- **Manufacturing and scale-up**
  - Tisagenlecleucel, first FDA-approved CAR T-cell therapy, established the manufacturing process for genetically engineered autologous cell therapies



Albinger N. et al. Gene Therapy. 2021.

Conclusions

- The fundamentals of pharmacodynamics allows the clinician and scientist to strategically deliver drugs for optimizing treatment to the patient
- Conventional routes of administration leveraged biopharmaceutical technology to greatly enhance drug availability
- Ongoing challenges consists of improving stability, PK, reducing immunogenicity, and off-target toxicities
- Strategies implemented to mitigate these challenges include drug modifications and environmental modifications

Thank you. Questions?

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Pharmacodynamics & Clinical Application of Therapeutics

Cancer Engineering

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