# 20.201 Mechanisms of Drug Action

## Lecture #19: PBPK

November 2, 2005

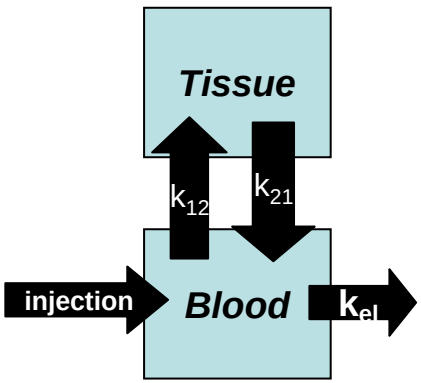
# Review of Lecture #18

- Began covering simple compartment models of PKs
- Discussed zero- and first-order kinetics in terms of implications for drug behavior in the body
- Derived rate expressions for 1- and 2-compartment models
- Began to develop the idea of stringing together one-compartment models into more complicated systems

# *Pharmacokinetic Behavior*

- **Two compartments with I.V. injection**

~ Injected drug distributes in blood “instantaneously”
~ Drug moves out of blood into tissue compartment: first-order (why?)
~ As blood concentration falls, higher tissue concentration drives return to blood (why?)
~ Examine plasma concentration versus time plot in this model

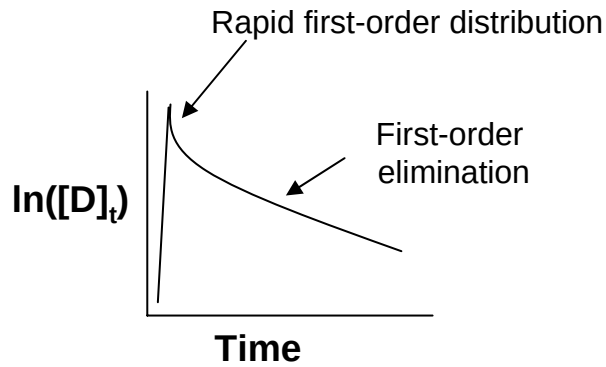


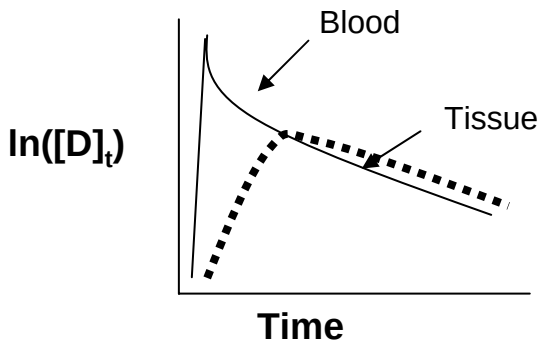

$$d\frac{[D]_p}{dt} = k_{21}[D]_{tis} - k_{12}[D]_p - k_{el}[D]_p$$

$$Integrate \Rightarrow [D]_{p_t} = Ae^{-\alpha t} + Be^{-\beta t}$$

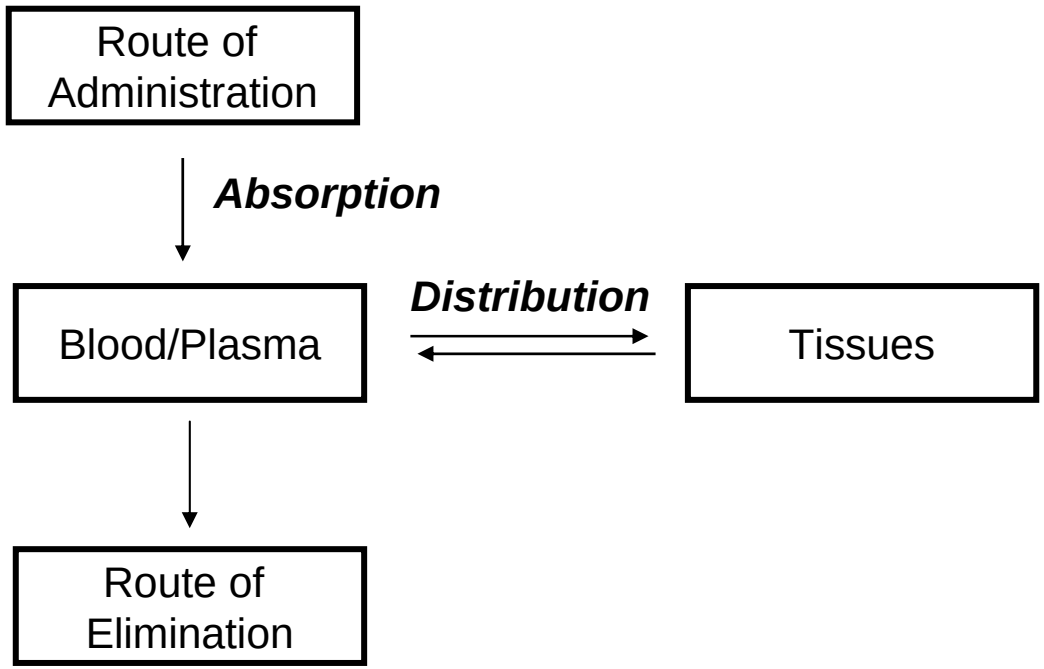
$$\alpha + \beta = k_{12} + k_{21} + k_{el} \qquad A = [D]_{p_0}\left(\frac{\alpha - k_{21}}{\alpha - \beta}\right)$$

$$\alpha \bullet \beta = k_{21} \bullet k_{el} \qquad B = [D]_{p_0}\left(\frac{k_{21} - \beta}{\alpha - \beta}\right)$$



# *Pharmacokinetics: Basic Concepts*




**Routes of administration**

(1) Enteral -
- oral
- sublingual
- rectal

(2) Parenteral -
- intravenous (iv)
- intramuscular (im)
- subcutaneous (sc)

(3) Other -
- inhalation
- topical
- transdermal

# PBPK Models: Pro's and Con's

• Two types of PK models:

~ Simple models:
- one and two compartments
- no physiological meaning to the compartments or the rate constants
- Example: rate constant for elimination from blood ($k_{el}$) has many contributions, including diffusion into tissues, excretion, metabolism

~ Physiological models:
- compartments represent biologically/physiologically real organs, tissues, excretion routes, etc.
- rate constants represent real biological processes, such as rate of metabolism

• PBPK models are developed to provide predictive tools for drug development and, more importantly, for risk assessment

~ PBPK's predict distribution to individual tissues and targets

~ PBPK models adapt to changes in physiological or health status; example: alterations in metabolism in liver disease

~ PBPK models typically involve scaling from rodents to humans

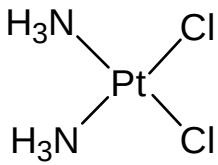
• Disadvantages:

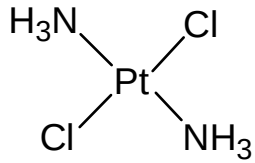
~ Huge amounts of data required, which means many experiments to define each parameter

~ Impractical for pharmacologically relevant data such as blood half-life, etc.

# *Cisplatin History*

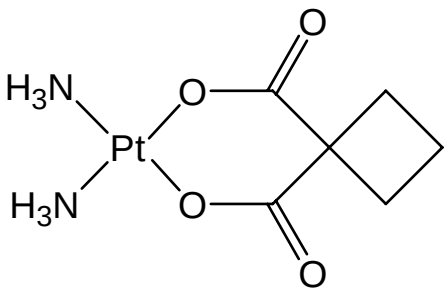
**Cisplatin**
*cis*-diamminedichloroplatinum(II)



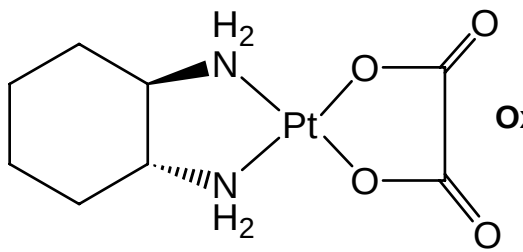




**Transplatin**
*trans*-diamminedichloroplatinum(II)

- Cisplatin is one the most widely used anticancer drugs on the market
- Clinically active against testicular, ovarian, lung and head/neck tumors
- Usually given in combination with other anticancer drugs
- Discovered by Barnett Rosenberg in the Dept. of Biophysics at Michigan State University
- Rosenberg was studying the growth of E. coli in electrical fields and observed bizarre, filamentous growth of the bacteria
- Fortuitously correlated bizarre growth with mutagenesis and DNA reaction; isolated active component from cell culture medium = platinum complexes; cisplatin most active



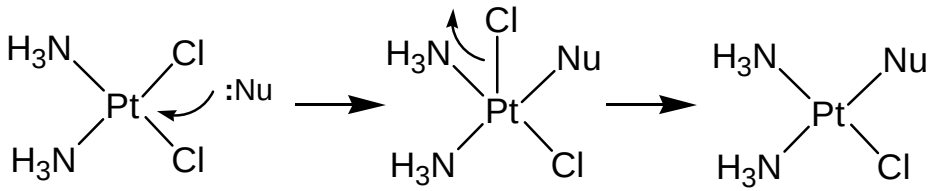

**Carboplatin**
*cis*-diammine(1,1-cyclobutane dicarboxylato)platinum(II)



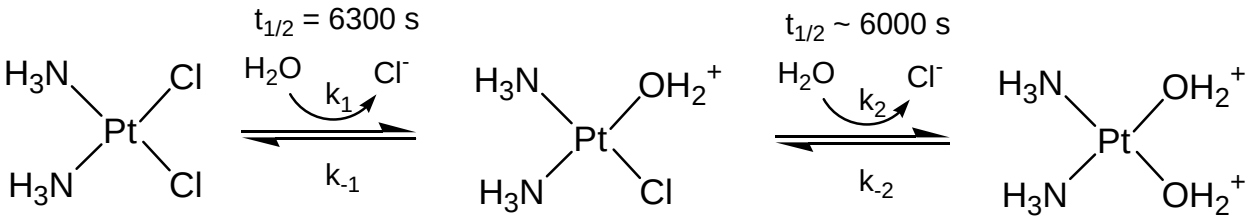

**Oxaliplatin**

# *Cisplatin Chemistry*

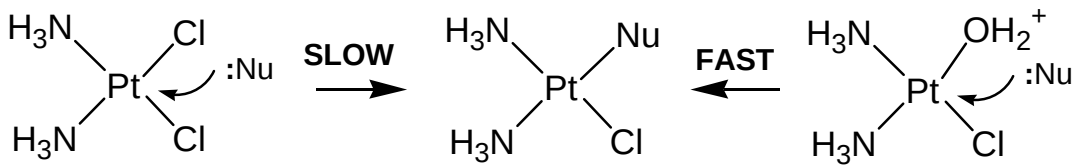
- Mechanism of action is believed to involve binding to DNA and disruption of replication and cell cycle
- Mechanism of action exploits simple chemistry: nucleophilic substitution reactions




- Cisplatin is a square planar inorganic complex with coordinate covalent bonds that readily undergo exchange reactions with other "ligands" such as water

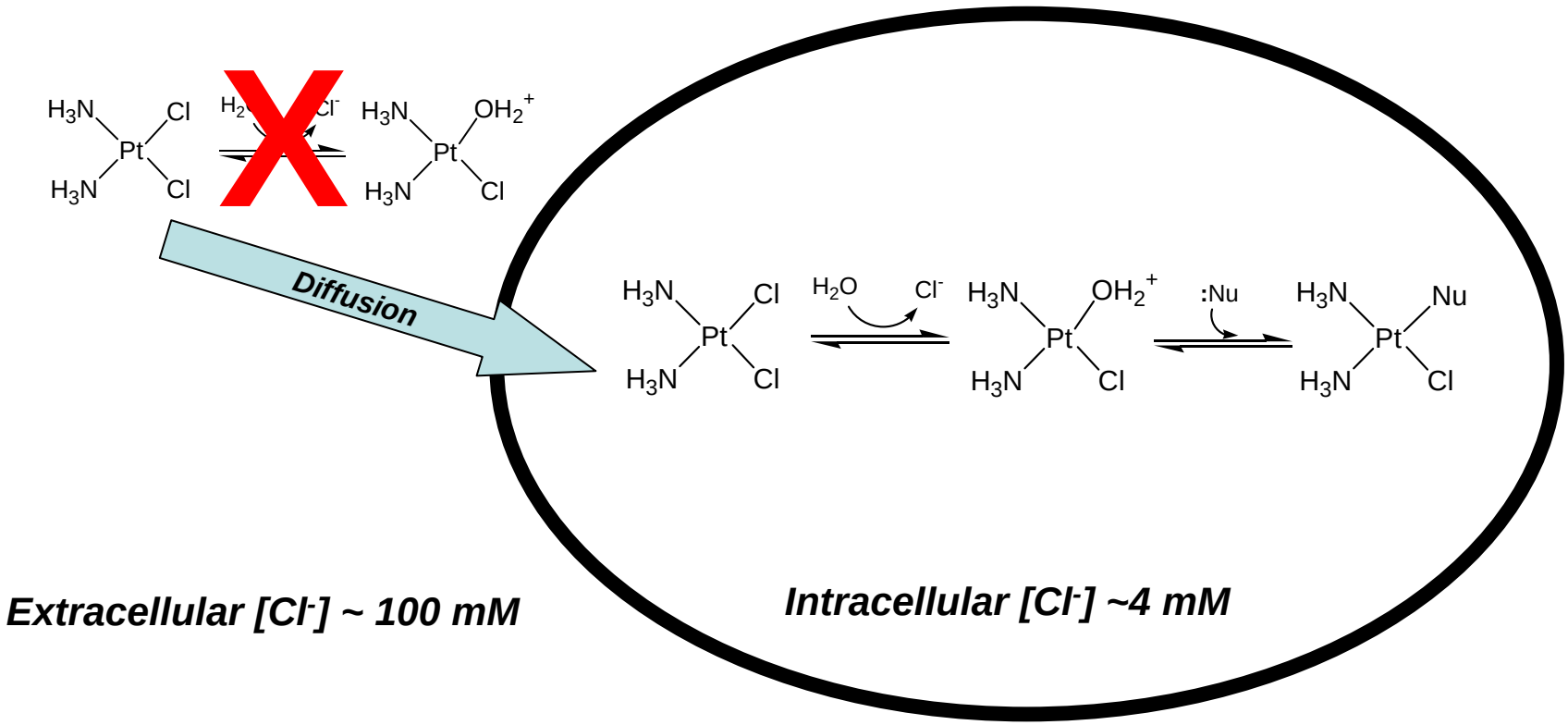



- Replacement of chloride ligands is slower than replacement of water ligands. Water concentration is 55 M, so even as a relatively weak nucleophile, water reacts to displace chloride followed by rapid displacement of water by biological nucleophiles (N in DNA, etc.)



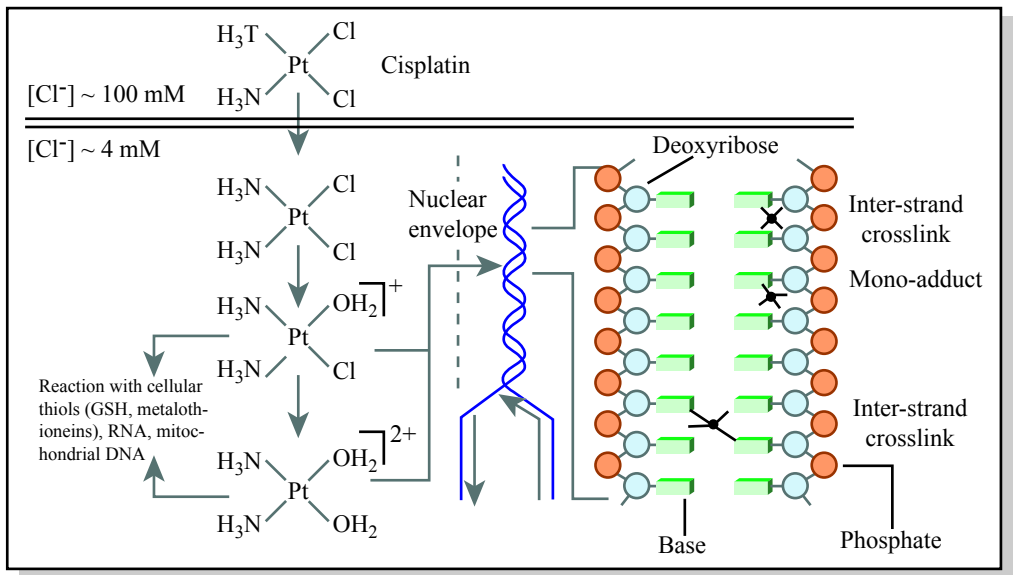
# *Cisplatin Biochemistry*

- High chloride concentration in plasma (~100 mM) inhibits aquation reaction
- Cisplatin diffuses across cell membranes (possible transporter in some cells)
- Low chloride concentration in the intra-cellular environment (~4 mM) leads to formation of aquated species that react rapidly with cellular nucleophiles (DNA, proteins, etc.)

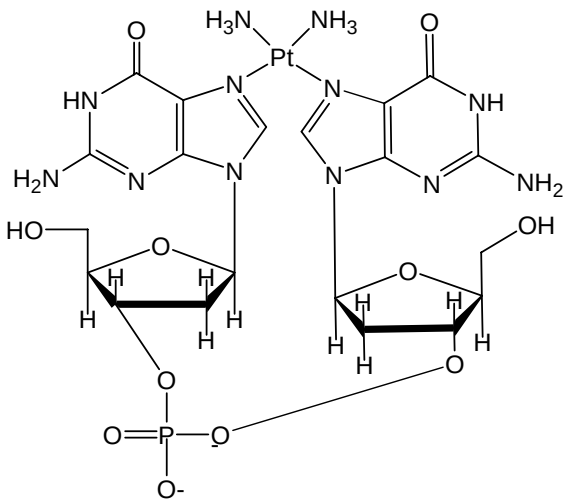


# *Cisplatin Biology*

- Low chloride concentration in the intra-cellular environment (~4 mM) leads to formation of aquated species that react rapidly with cellular nucleophiles (DNA, proteins, etc.)
- DNA adducts:
  - ~ intra-strand GG, AG and GXG cross-link (>95%)
  - ~ inter-strand GG cross-link (<5%)
- Clinical correlate: transplatin is ineffective as an antitumor agent; forms DNA adducts -- mainly mono adducts, GXG and inter-strand adducts; but not GG intra-strand cross-links
- So why is cisplatin more effective as an antitumor agent?




After John Essigmann, figure by MIT OCW.



## *Cisplatin-DNA Adduct Structures*

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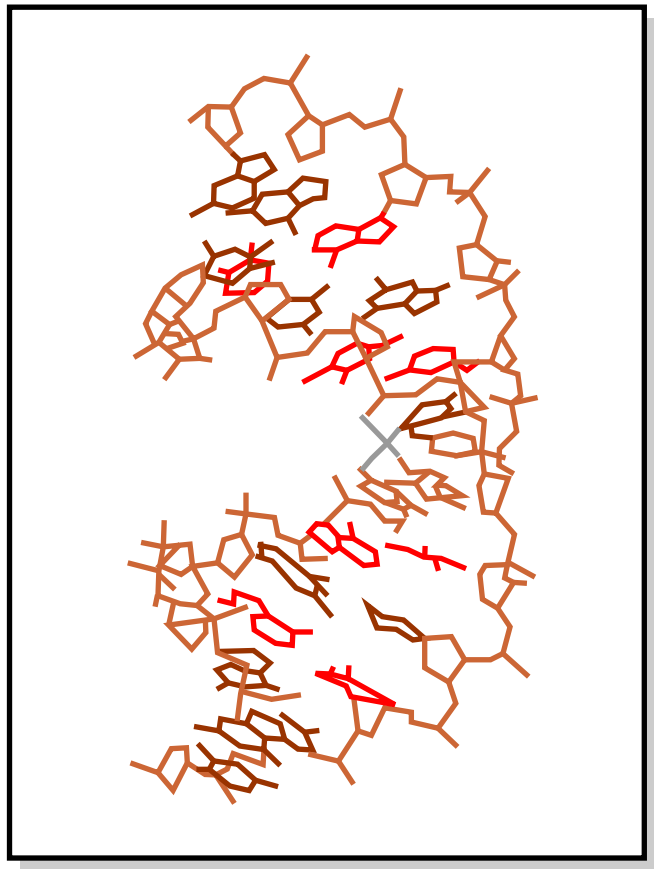

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# *Cisplatin Biology*

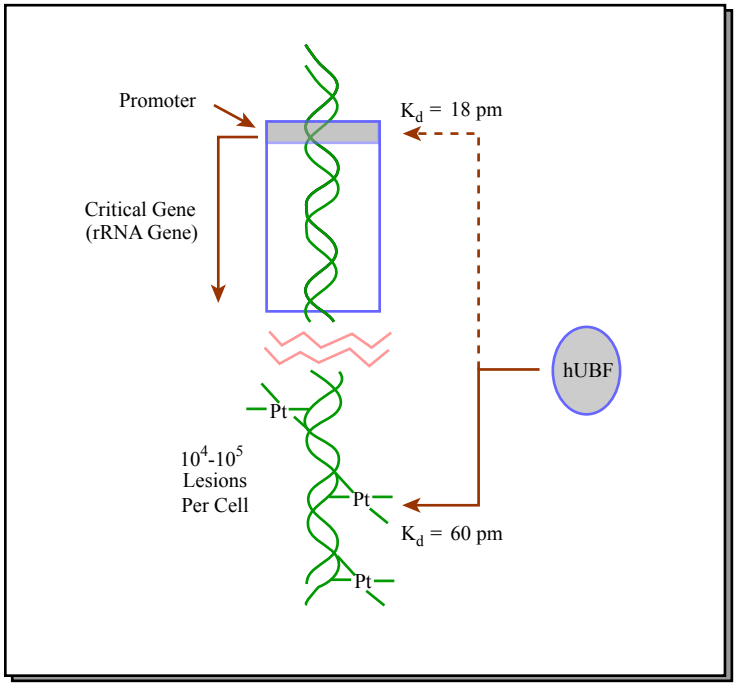


Figure by MIT OCW.

Fig. 4. The transcription factor hijacking model: in a therapeutic regimen including cisplatin, approximately 104ñ105 adducts form per cell and the cisplatin adducts sequester hUBF away from its promoter, thereby, disrupting the transcription of ribosomal genes that may be critical for cell survival.

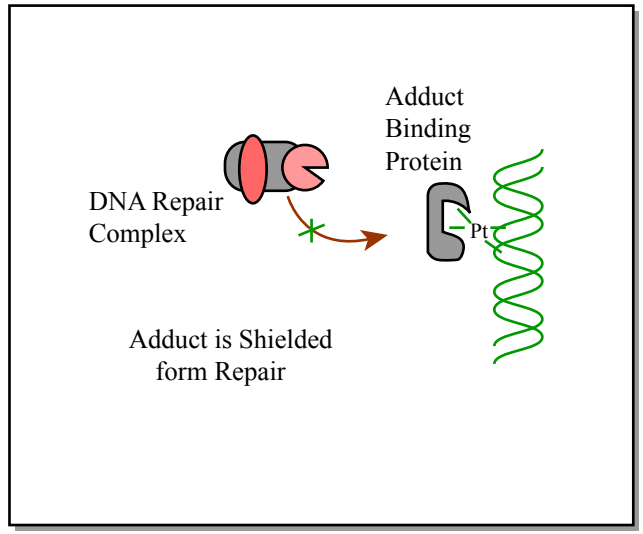


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Fig. 5. The repair shielding model: the adduct binding protein recognizes the cisplatin adducts and can inhibit their repair by physically blocking the access to other repair proteins. The cisplatin adducts persist in DNA, thereby, potentiating their toxicity.

**John Essigmann Figures!**

# Building a PBPK Model:
# Step one - Define the compartments

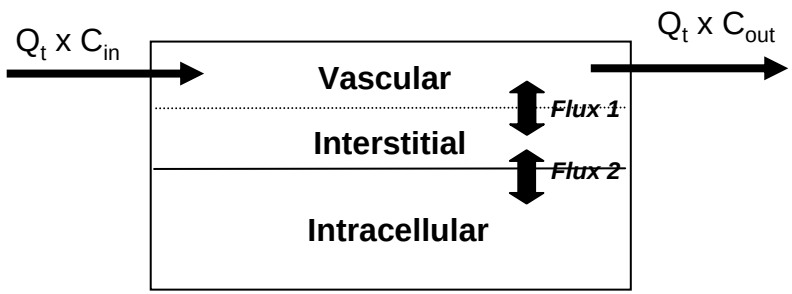
- Construct a flow diagram based on compartments with blood compartment connecting all others

- Define compartments as individual organs or groups of organs with similar behavior

  ~ Target organ/site for the chemical or drug
  ~ Must always have blood as a compartment (transport link to all other compartments)
  ~ Routes of excretion: kidney, bile, pulmonary for volatile organics, sweat….
  ~ High affinity binding sites or depot tissues: adipose tissue for lipophilic compounds
  ~ Low affinity distribution sites that may be significant due to organ size (skin, muscle, etc.)
  ~ Sites of metabolism: liver, lungs, intestinal epithelium…
  ~ Sites of toxicity

- String compartments together by blood flow and in physiologically relevant order (blood flow from gut goes to liver and then into general circulation!)

- Define and assign sub-compartments for each compartment:



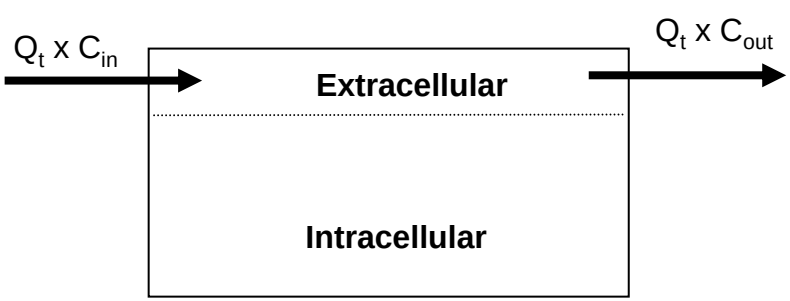

Flux = P•A•ΔC (liters/hour)

# Building a PBPK Model:
# Step one - Define the compartments

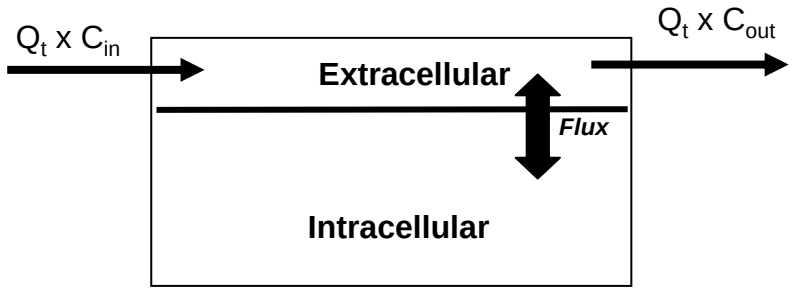
- Sub-compartments are of two types

  ~ ***Flow limited:*** $P \cdot A >> Q_t$
  - rate of entry of chemical into interstitial and intracellular spaces is faster than the rate of blood flow into the compartment
  - Most common type of sub-compartment due to leaky capillaries, rapid diffusion or carrier transport (saturation problems!!)
  - Important to note that $C_{out} = C_f$, where $C_f$ is the concentration of unbound/free chemical in the tissue; equilibrium is established early in the entrance of blood into the compartment

  ~ ***Diffusion or membrane limited:*** $P \cdot A << Q_t$
  - rate of entry of chemical into interstitial and intracellular spaces is slower than the rate of blood flow into the compartment
  - Occurs with blood-brain barrier or transporter saturation
  - Usually applies to movement into cells: rarely is movement from vascular to extra-cellular space hindered by transport

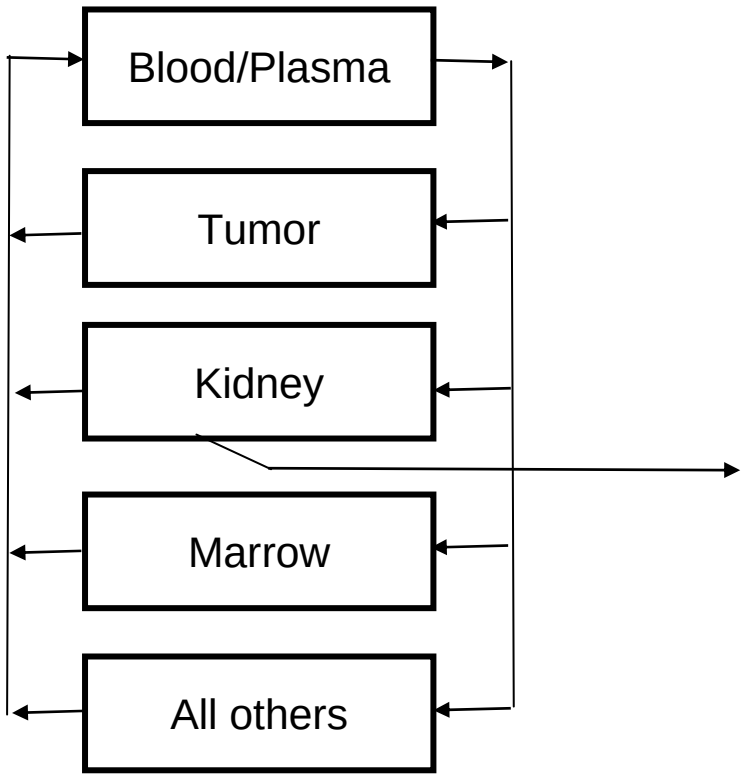



***Typical flow limited compartment***




***Typical diffusion limited compartment***

# Building a PBPK Model:
# Step two - construct a flow diagram




- Must have blood compartment
- Tumor is the “target” tissue for efficacy
- Kidney and bone marrow are targets for toxicity
- All other tissues lumped together as one compartment

# Building a PBPK Model: Step two - Define the parameters

• Now define parameters for each compartment, process and physiological facet of the model

• ***Anatomical parameters***:

~ Abundance of data for numerous animal species published in tables in various sources
~ Volume is very important to our calculations
~ Anatomical parameters can be scaled (allometric scaling) for different animal species
~ Example: $y = a \cdot W^b$
- **y** is the parameter of interest, such as organ volume
- **W** is body weight of the animal
- **a** and **b** are empirically determined constants for a given species
~ Organ volume tends to be linearly related to body weight: Volume = a•W
~ Blood flow and $V_{max}$ tend to scale to the 3/4 power of weight: Flow = $a \cdot W^{3/4}$
~ Rate constants tend to scale to the -1/4 power of weight: $k = a \cdot W^{-1/4}$

• ***Physiological parameters***: most important here are blood flow rates to different organs

• ***Thermodynamic parameters***:
~ Assumes equilibrium is established in the model; practical but not realistic
~ Partition coefficients for distribution from blood to tissue and back

• ***Transport parameters***: P•A determines rate of diffusion; active transport and saturation of transporters

• ***Metabolic parameters***: rates of metabolism in different tissues; often use M&M kinetic assumptions

• ***Elimination and excretion parameters***: clearance calculations

• ***Uptake and delivery parameters***: dosing functions are important; defines rate at which chemical enters the body.

# Building a PBPK Model:
# Step two - Define the parameters for cisplatin

- ***Anatomical parameters***
- ***Physiological parameters***: most important here are blood flow rates to different organs

- ***Thermodynamic parameters***:
  - ~ Partition coefficients for distribution from blood to tissue and back
  - ~ Tissue:Plasma partition coefficient ~ 1: Good assumption since cisplatin freely diffuses across cell membranes
- ***Transport parameters***: P•A determines rate of diffusion; active transport and saturation of transporters
  - ~ Good assumption: cisplatin freely diffuses; no transporter (one may exist in kidney!)
  - ~ Thus have a flow-limited situation

- ***Metabolic parameters***: rates of metabolism in different tissues; often use M&M kinetic assumptions
  - ~easy: no enzymatic metabolism
  - ~ rate constants of biotransformation are the rate constants for the chemical reactions outlined earlier

- ***Elimination and excretion parameters***: clearance calculations
  - ~Cisplatin excreted mainly via the kidney
  - ~ Measure clearance: $Cl_{kidney}$ = mg drug in urine over time interval/AUC over same time interval
  - ~ OR: assume $Cl_{kidney}$ = glomerular filtration rate; good assumption since most cisplatin is filtered at the glomerulus and not secreted into the tubule. GFR's from parameter tables

- ***Uptake and delivery parameters***: dosing functions are important; defines rate at which chemical enters the body.

# Building a PBPK Model:
# Step two - Anatomical and physiological parameters for cisplatin

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Please see Table 1 in Farris, et al. *Tox Lett* 43 (1988): 117-37.

# Building a PBPK Model:
# Step two - Metabolic parameters for cisplatin



Table removed due to copyright restrictions.
Please see Rate Constant for the Biotransformation of Cisplatin table in Farris et al. *Tox Lett* 43 (1988): 117-37.

# Building a PBPK Model:
# Step three - Write mass balance equations