AGENDA

09:00	Introduction
09.15	Lecture 1 (Historical overview of prodrugs)
10.45	Coffee Break
11.00	Lecture 2 (Bioorthogonal prodrugs 1)
12:30	Lunch
13:30	Lecture 3 (Bioorthogonal prodrugs 2)
15:00	Coffee Break
15:30	Lecture 4 (Challenges to progress metal-activated prodrugs into the clinic)
17:00	Go to hotel
19:00	Dinner (TBC)

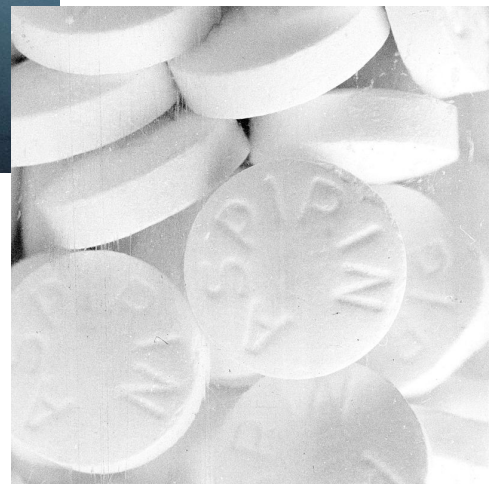
Historical overview of prodrugs

Basic concepts

- A **drug** is a chemical substance, typically of known structure, which, when administered to a living organism, produces a biological effect.

- **A pharmaceutical drug**, also called a medication or medicine, is a chemical substance used to treat, cure, prevent, or diagnose a disease or to promote well-being.

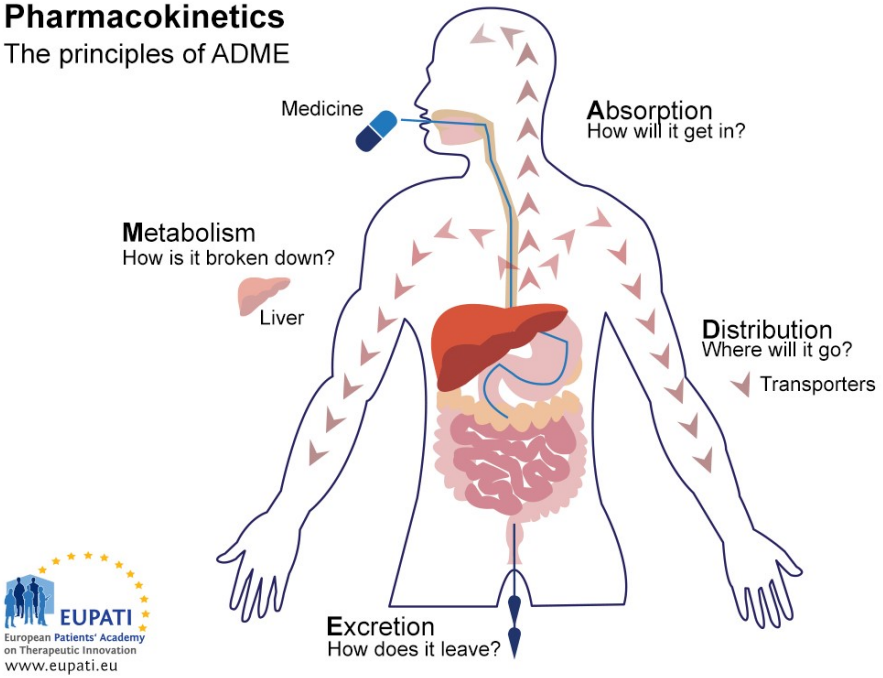
Caffeine is a psychoactive drug



Basic concepts

- **Pharmacokinetics** (PK) is the study of how an organism affects a drug, whereas **pharmacodynamics** (PD) is the study of how the drug affects the organism.

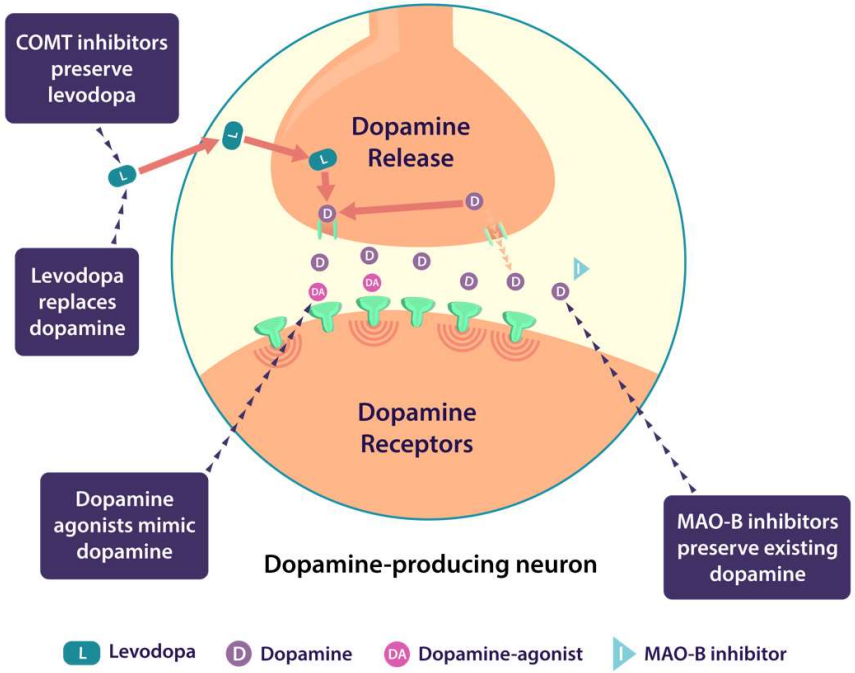
- **IUPAC definition of PK:** Process of the uptake of drugs by the body, the biotransformation they undergo, the distribution of the drugs and their metabolites in the tissues, and the elimination of the drugs and their metabolites from the body over a period of time.



Basic concepts

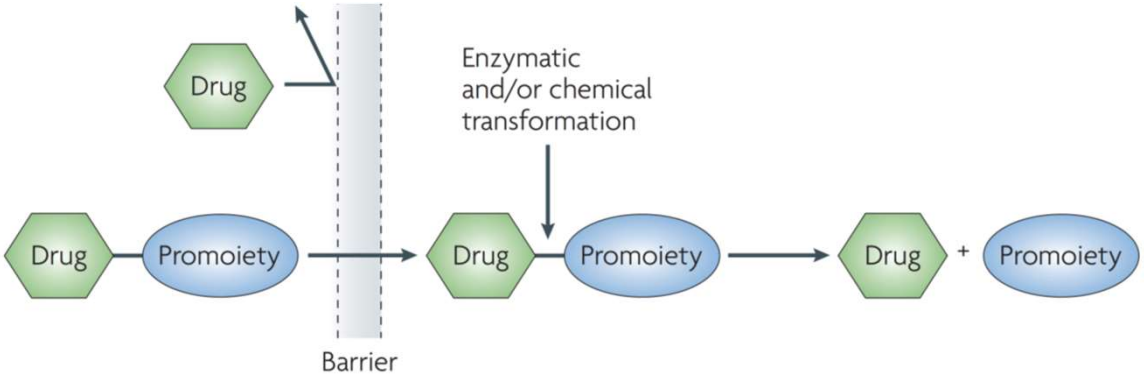
- **Pharmacodynamics** (PD) is the study of the biochemical and physiologic effects of drugs. PD places particular emphasis on dose–response relationships, i.e. the relationships between drug concentration and effect.

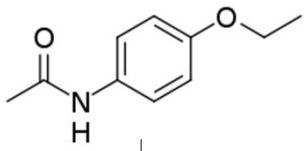
- **IUPAC definition of PD:** Study of pharmacological actions on living systems, including the reactions with and binding to cell constituents, and the biochemical and physiological consequences of these actions.



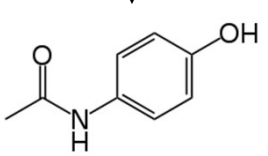
Definition of prodrugs

- **Prodrugs** are molecules with little or no pharmacological activity in their own right but have a built-in structural lability, whether by chance or by design, that permits bioconversion in vivo.





Phenacetin
(analgesic)



Paracetamol
(analgesic)

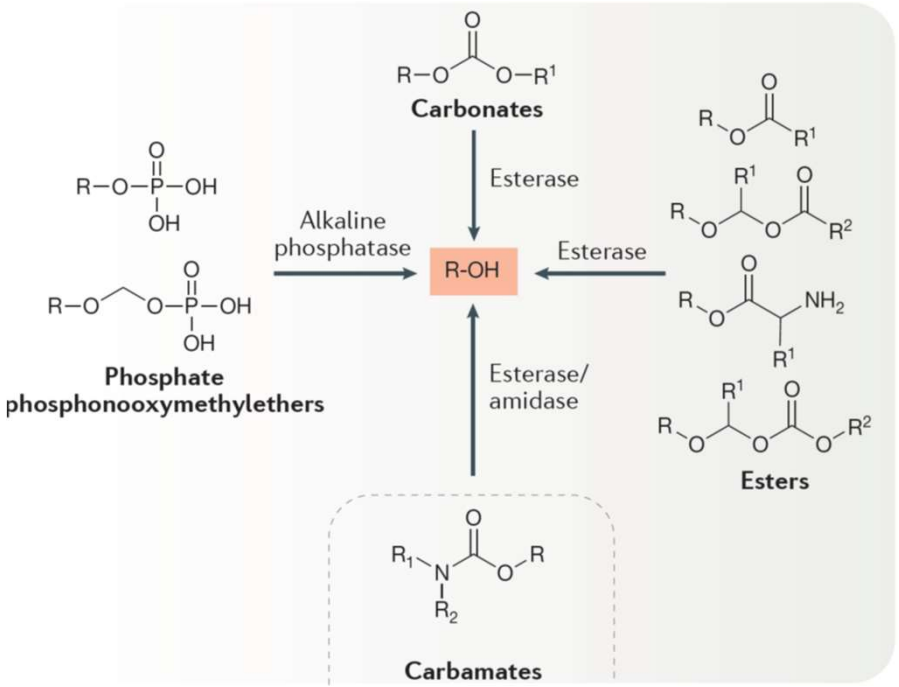
- While formally recognized by Adrian Albert in 1958, prodrug strategies have their roots in the 1900s, e.g. phenacetin.

- Approx. 10% of all marketed drugs worldwide can be considered prodrugs.

Chemistry of prodrugs

- Most prodrug approaches require a ‘structural handle’ on the drug, which are typically heteroatomic groups. Most common functional groups amenable to prodrug design include carboxylic, hydroxyl, amine, phosphate/phosphonate and carbonyl groups

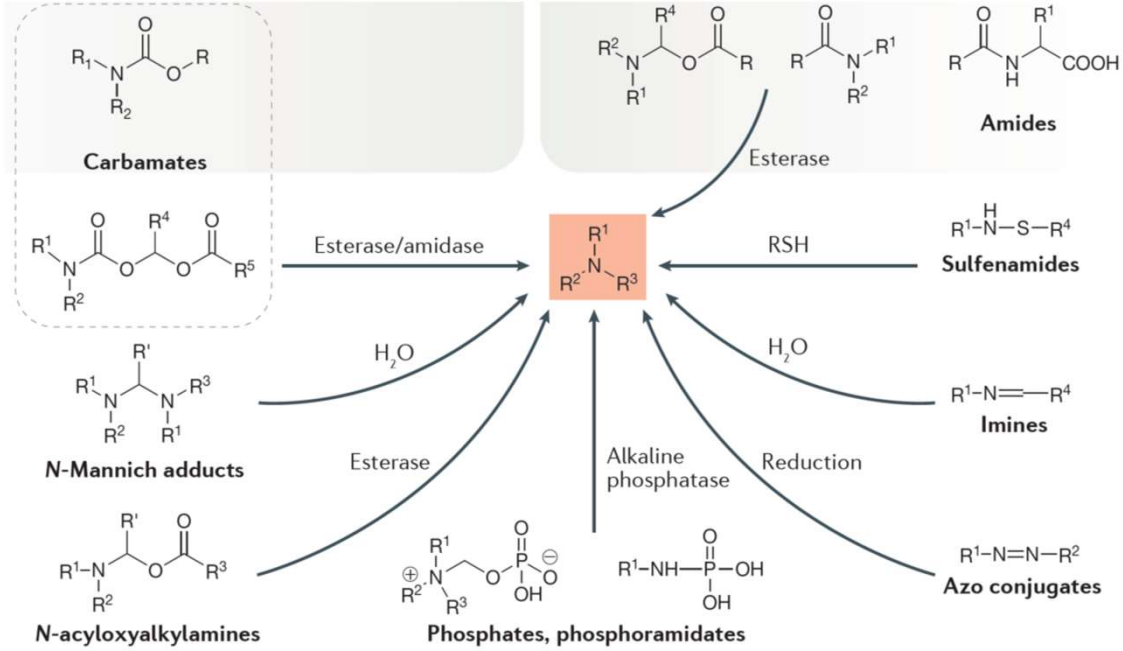
- Prodrugs typically produced via the modification of these groups include esters, carbonates, carbamates, amides, phosphates and oximes.



Chemistry of prodrugs

- Most prodrug approaches require a ‘structural handle’ on the drug, which are typically heteroatomic groups. Most common functional groups amenable to prodrug design include carboxylic, hydroxyl, amine, phosphate/phosphonate and carbonyl groups

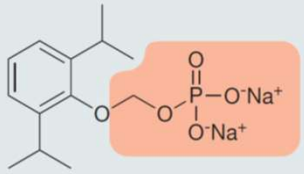
- Prodrugs typically produced via the modification of these groups include esters, carbonates, carbamates, amides, phosphates and oximes.



Why do we make prodrugs?

- Prodrug strategies are often used to overcome deficiencies in the physicochemical properties of a molecule that limit formulation options and result in unacceptable biopharmaceutical performance.

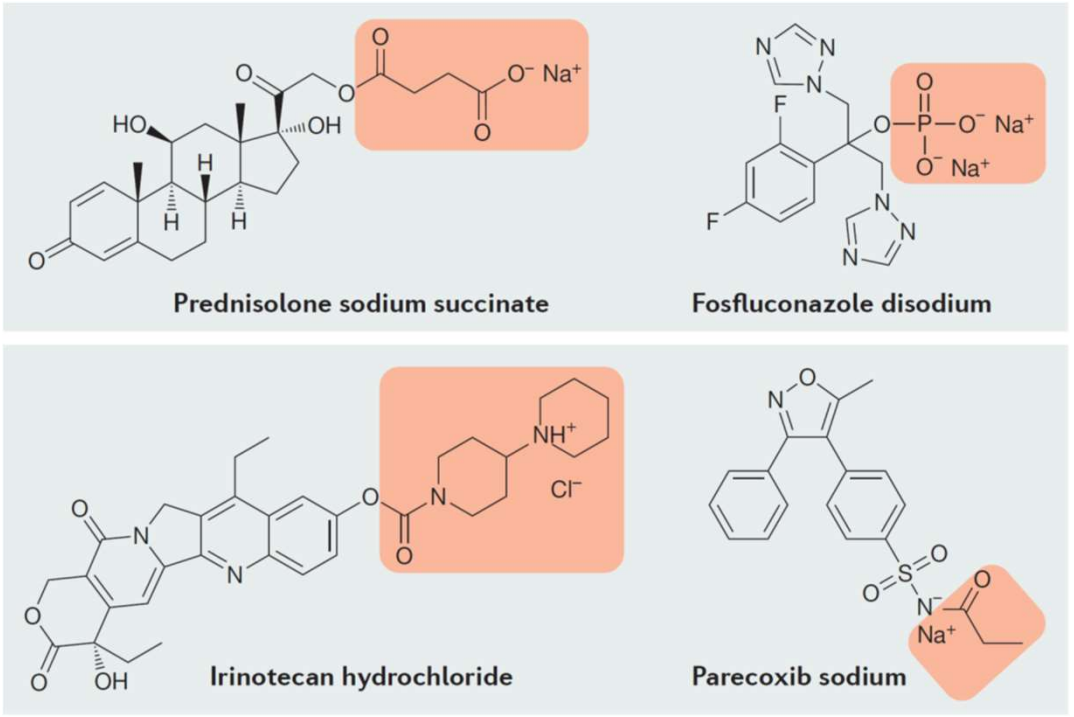
- Example: *sufficient solubility of a drug is essential for parenteral or injectable drug dosing*.

No.	Prodrug (drug name) and structure (promoiety in orange box)	Indication (mechanism of action)	Prodrug strategy and improved property	Approval date
3	 Fospropofol (Lusedra, fospropofol disodium)	Anaesthetic (sedative–hypnotic agent)	• Phosphonooxymethyl ester • Improved aqueous solubility of propofol from 150 µg mL^{-1} to ~500 mg mL^{-1} (REFS [27,29])	12 Dec 2008

Improving oral delivery

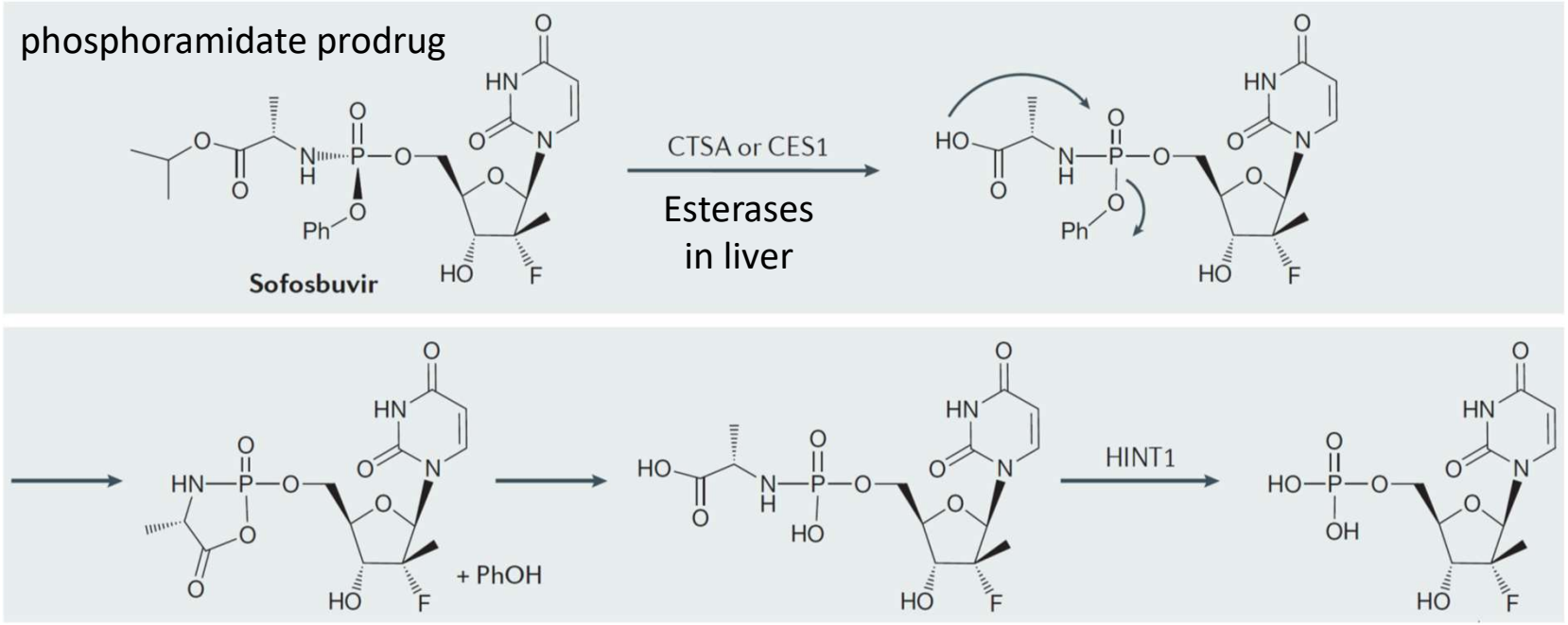
- Aqueous solubility is one of the most important properties, regardless of the administration route of a drug

- A drug with low solubility may face low and variable oral bioavailability, which leads to an unpredictable clinical response. Strategies to improve solubility for oral administration are similar to those used for solubilizing drugs for parenteral administration



Improving PK and PD

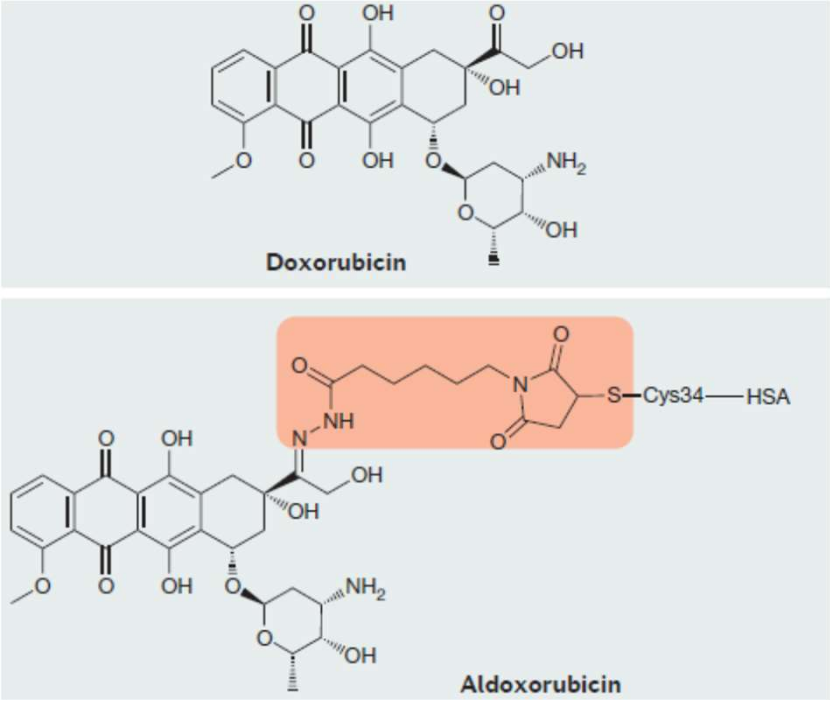
- The ‘ideal’ prodrug yields the parent drug with high recovery ratios, with the promoiety being non-toxic.



BYPRODUCTS: Isopropanol + phenol + alanine

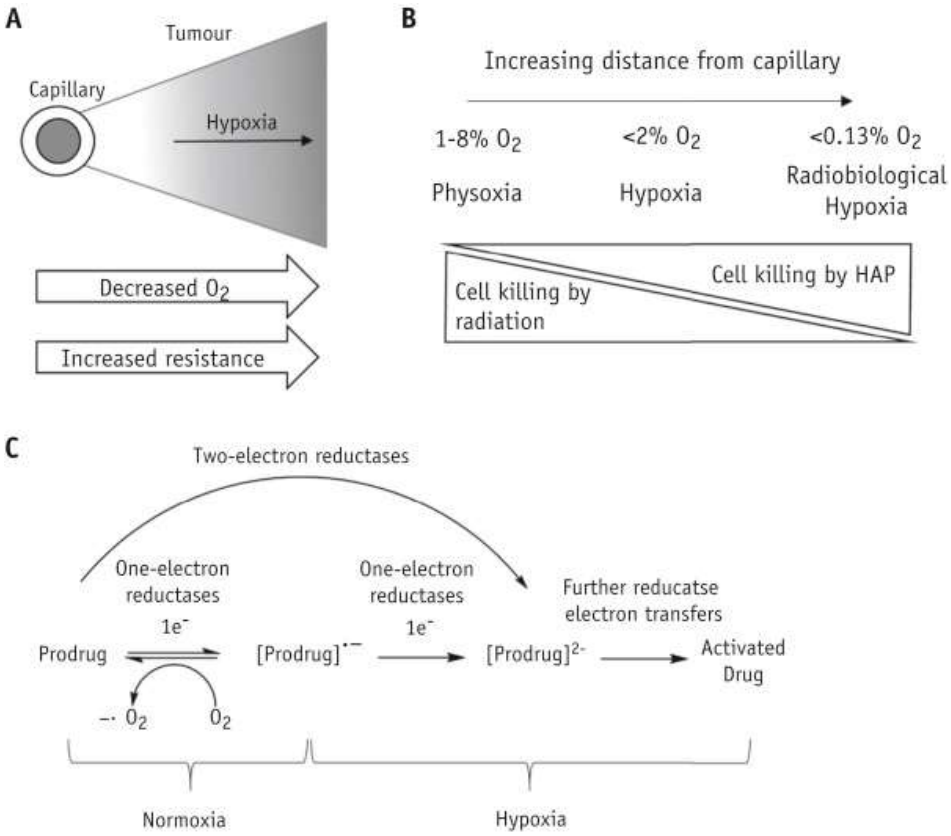
Targeting cancer: pH

- Site-selective prodrug activation and release of the active drug can be achieved by exploiting the physiological conditions of the target site if they differ from conditions in the rest of the body.
- One such condition is the acidic environment found in tumour tissue, endosomes and lysosomes, which can be used for site-selective conversion of acid-sensitive bonds, such as an imine and hydrazone, in anticancer prodrugs



Targeting cancer: hypoxia

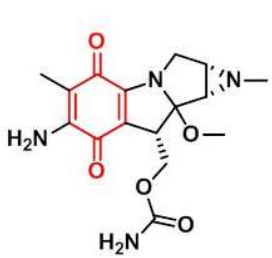
- Hypoxia-Activated Prodrugs (HAPs) are prodrugs that target regions of hypoxia within tumours.
- Tumour hypoxia contributes significantly to treatment failure and relapse among cancer patients. Hypoxic zones of solid tumours are not accessible for most antitumor agents (low penetration beyond 50-100 micrometers from capillaries) and the lower nutrient and oxygen supply to cells cause them to divide more slowly.



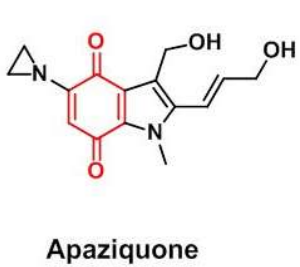
Targeting cancer: hypoxia

- Despite the promising features of this approach, no HAP has yet received regulatory approval.
- Most HAPs were poorly tolerated by patients and trials terminated.
- No trials currently ongoing.

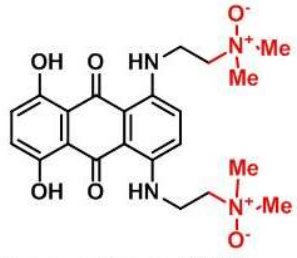
Hypoxia-activated prodrugs that didn't make it



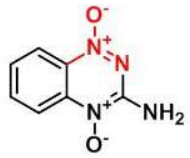
Porfiromycin (NCI)



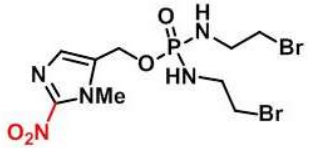
Apaziquone (Spectrum)



Banoxantrone (NCI)



Tirapazamine (Sanofi/Aventis)

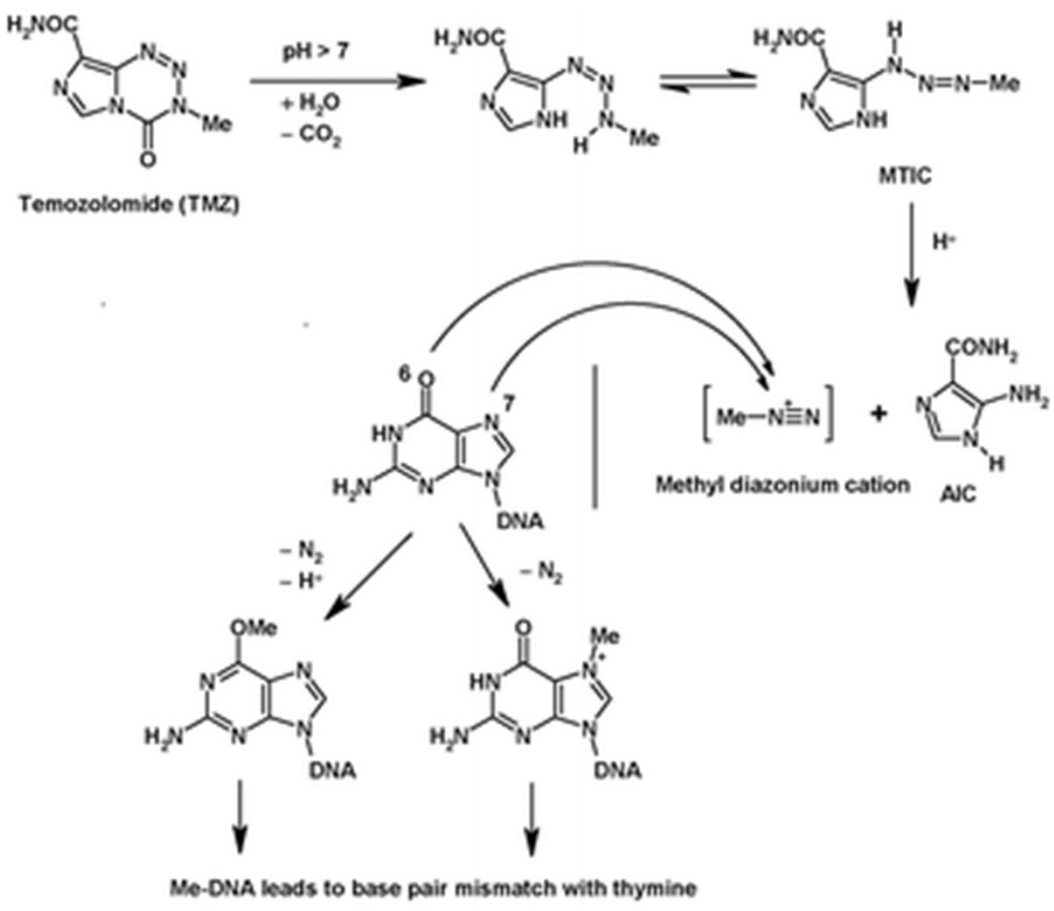


Evofosfamide (Threshold)

Despite a compelling biochemical rationale and much work by many, no hypoxia-activated prodrug has yet been FDA- or EMA-approved

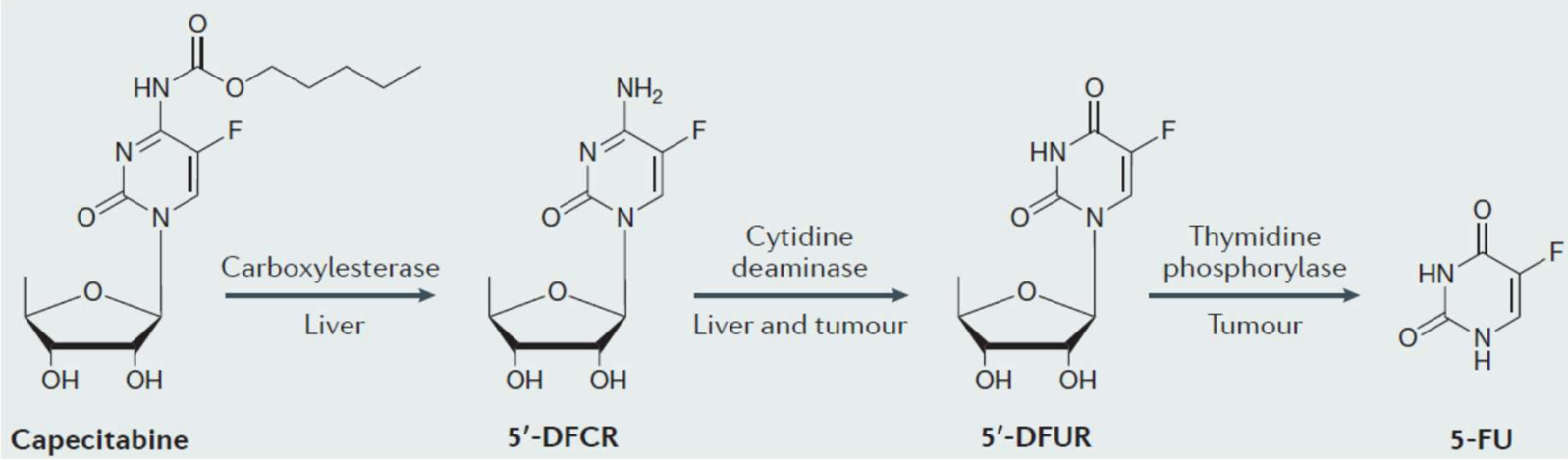
Targeting cancer: hypoxia? pH?

- Temozolomide is an oral chemotherapy prodrug used to treat some brain cancers.
- 2nd-line treatment for astrocytoma and 1st-line treatment for glioblastoma multiforme.
- TMZ is quickly and almost completely absorbed from the gut, and readily penetrates the BBB: [TMZ] cerebrospinal fluid is 30% of that of blood plasma.



Targeting cancer: Site-specific enzymes

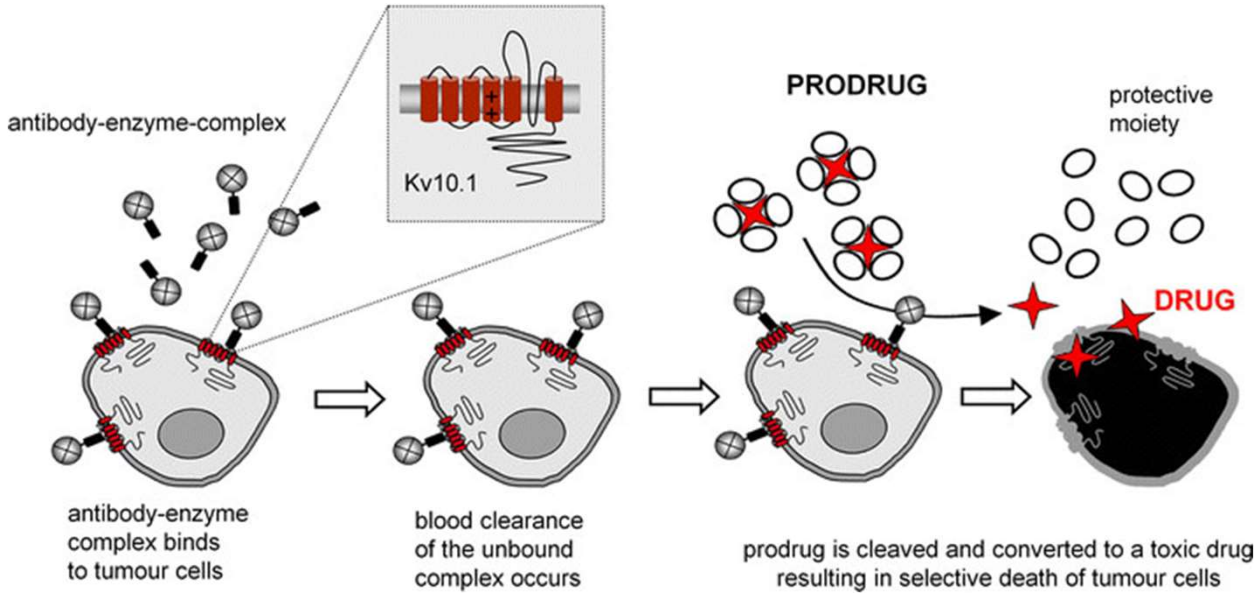
- An approach to overcome unwanted gastrointestinal side effects led to the rational discovery of capecitabine, an oral prodrug that requires three enzymatic steps to release 5-FU: carbamate hydrolysis, conversion by cytidine deaminase, and the release of 5-FU by thymidine phosphorylase.



- 5-FU concentration in tumour tissue was 2.5-fold higher than in healthy tissue and 14-fold higher than in plasma in advanced breast cancer patients

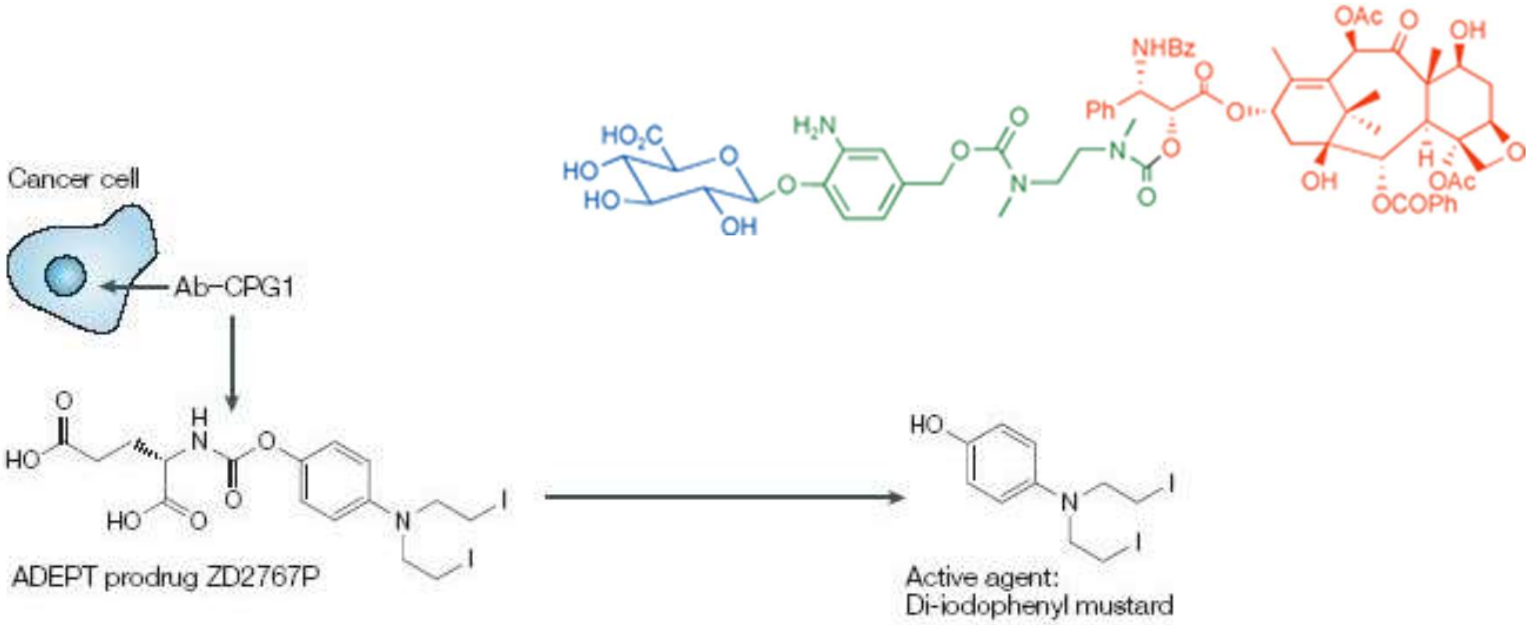
Targeting cancer: ADEPT

- **Antibody-directed enzyme prodrug therapy** (ADEPT) is a targeted strategy that employs an antibody against a tumour antigen covalently linked to an enzyme. Parental administration results in selective binding to the tumour. The enzyme then convert prodrugs to the active form at the tumour site.



Targeting cancer: ADEPT

- **Prodrugs** designed for ADEPT strategies can be activated by a wide range of enzymes that are not present in humans (typically bacterial) such as reductases, glycosidases (β-glucuronidases) or amidases.



Exercise

- Rapamycin is a protein protein interaction inhibitor that targets the protein complex mTORC1 by binding between FKBP12 and mTOR but has poor solubility
- The north region has been modified with different chemical groups to improve PK properties without affecting PD properties.
- Which groups would you modify to make a prodrug?