evropský sociální fond v ČR
EVROPSKÁ UNIE
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OP Vzdělávání pro konkurenceschopnost
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Název: Doxorubicin, anticancer drug, usage, toxicity

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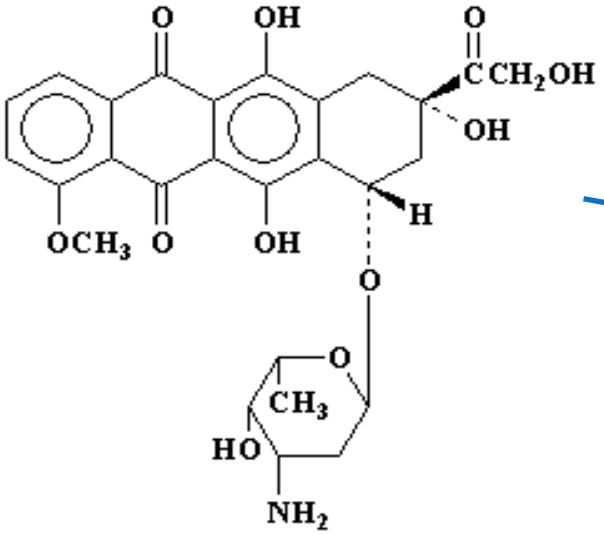
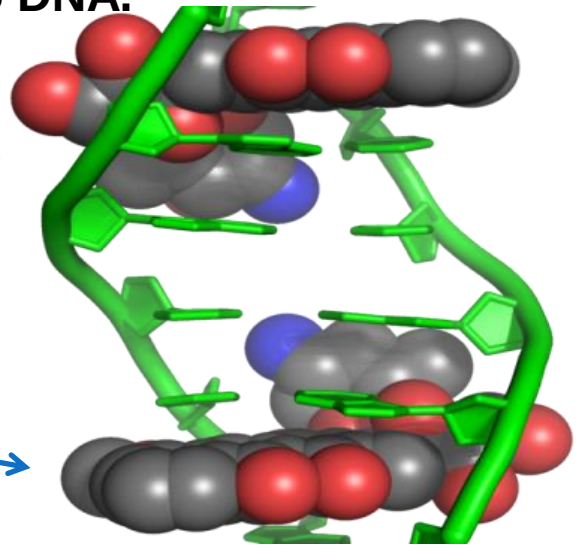
Název projektu: Mezinárodní spolupráce v oblasti "in vivo" zobrazovacích technik

Doxorubicin

- **Broadband anthracycline antibiotic, firstly isolated in 1950 from bacteria *Streptomyces peucetius*.**
- **One of the most used and the most powerful natural anticancer drug.**
- **It is useful in both monotherapy and with other cytostatics as well.**
- **Mechanism of effect – intercalation into DNA.**
- **It is fluorescent active.**
- **<u>Negative side-effects</u>.**





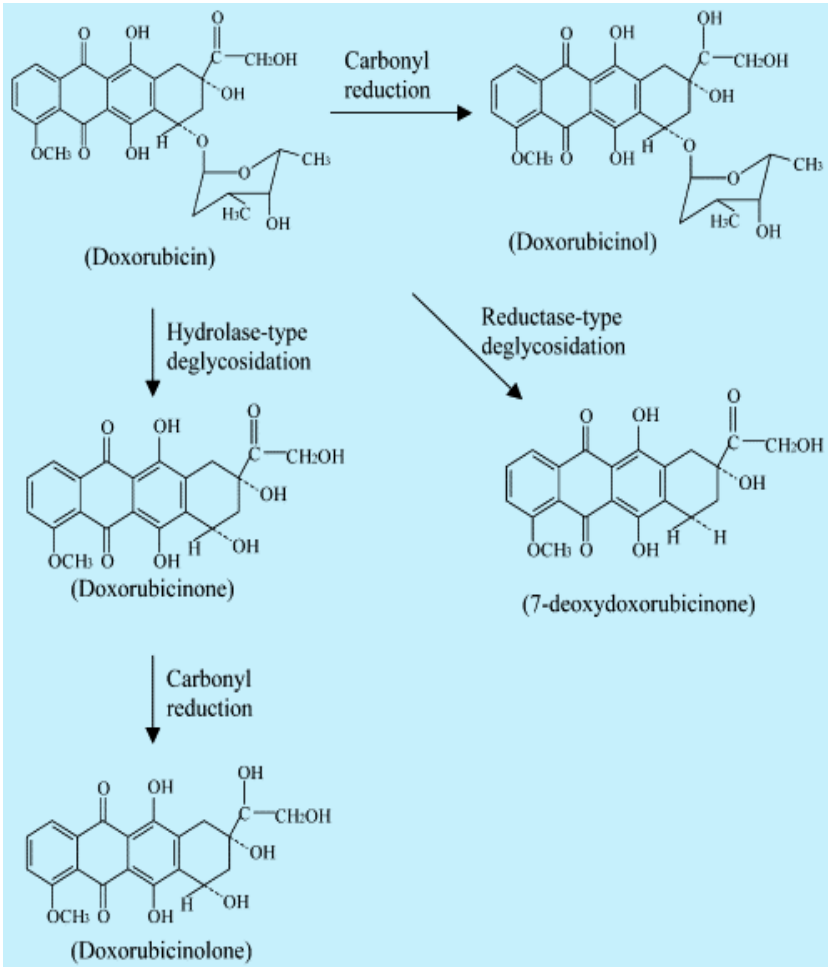
Interkalace DNA doxorubicinem

Negative side-effects: metabolization

- The most frequent transformation of DOXO is in liver, and excretion by primary bile.

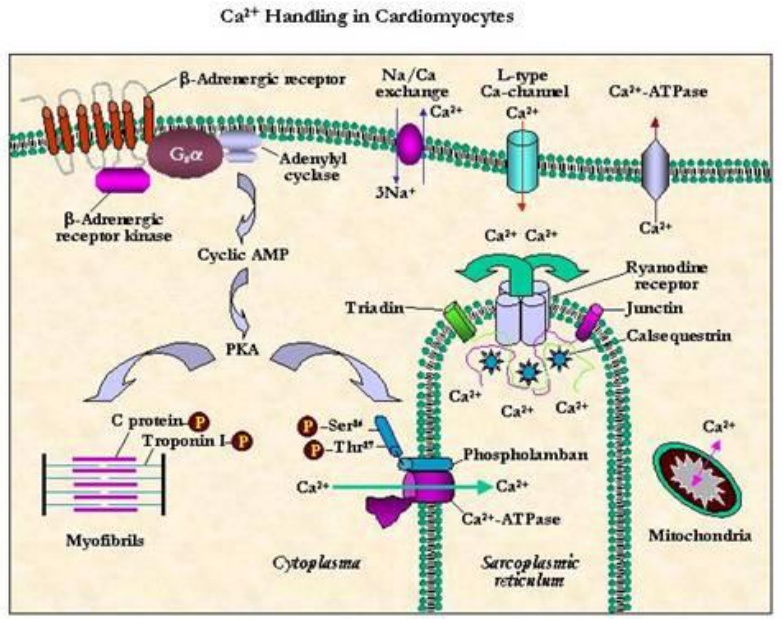
Primary metabolite – **doxorubicinol** has clinical importance, because it shows similar effects as doxorubicin.

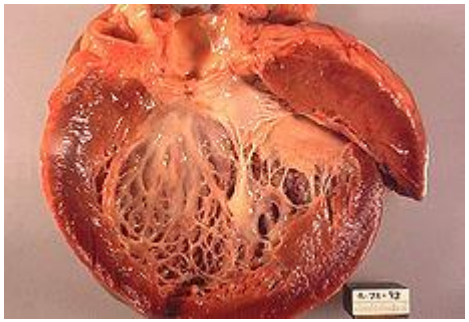
- **Doxorubicinol** and other metabolites – **doxorubicinon, doxorubicinolon, 7-deoxydoxorubicinon** or **7-deoxydoxorubicinolon** probably contributes into the free radicals forming and thus to higher occurrence of negative side-effects.

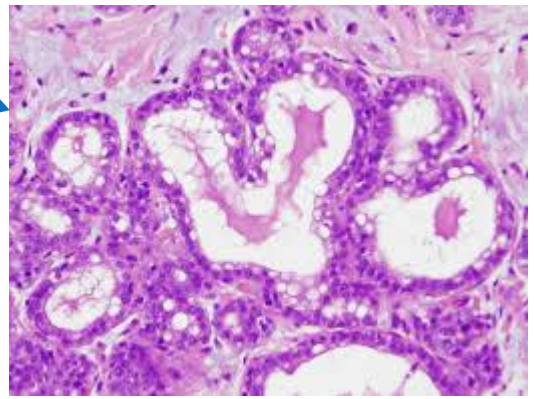


Detection of cardiomyopathy

- The golden standard for detection of acute doxorubicin induced cardiotoxicity is endomyocardial biopsy of the right ventricle because of its high sensitivity and specificity.







- Endomyocardial tissue from the right ventricle will show typical histopathological changes, including vacuolization of the cytoplasm, loss of myofibrils and distention of the sarcoplasmic reticulum and T-tubules.

Doxorubicin-induced cardiomyopathy

- The induction of free radical production is the best described major mechanism through which doxorubicin injures the myocardium.

- The heart's unique vulnerability to oxidative stress has given this aspect of doxorubicin induced **cardiomyopathy** an overwhelming prominence in the literature.

- Over the past thirty years, the understanding of how free radicals are generated and how they damage the heart has evolved from a purely chemical reaction to a molecular understanding of how enzymes such as **nitric oxide synthases** (NOS) and **NAD(P)H oxidase** interact with doxorubicin and induce oxidative stress.

Drugs – with high DOXO toxicity

- The first DOXO drug is administered intravenously, as the hydrochloride salt.
- It may be sold under the brand names **Adriamycin PFS, Adriamycin RDF,** or **Rubex**

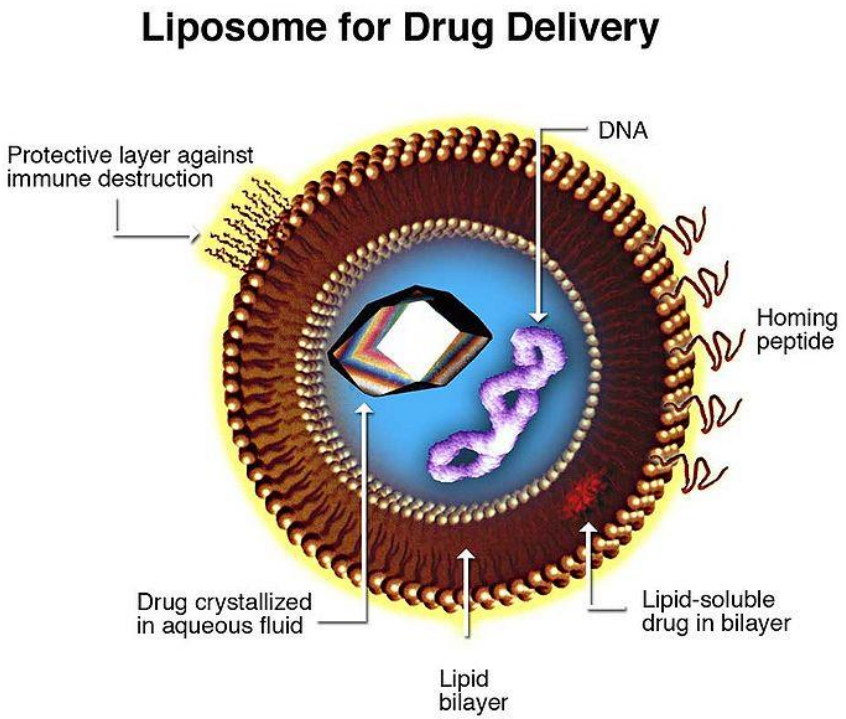
- One of Adriamicine PFS warnings: **"This medication must be given slowly into a vein only. It is very important not to inject this medication into a muscle or beneath the skin. If this medication accidentally leaks into surrounding tissue, the skin/muscle may be severely damaged. Notify your doctor immediately if redness, blistering, sores, pain, or swelling occur at or near the injection site."**

http://www.webmd.com/drugs/drug-6666-Adriamycin+PFS+IV.aspx?drugid=6666&drugname=Adriamycin+PFS+IV

Drugs - Reduction of DOXO Toxicity

- For reducing of the acute toxicity the new forms of this drugs has been developed
- A liposome is an artificially-prepared vesicle composed of a lipid bilayer. The liposome can be used as a vehicle for administration of nutrients and pharmaceutical drugs

- Doxorubicin is thus available in liposome-encapsulated forms as **Doxil** (United States), **Caelyx** and **Myocet.**

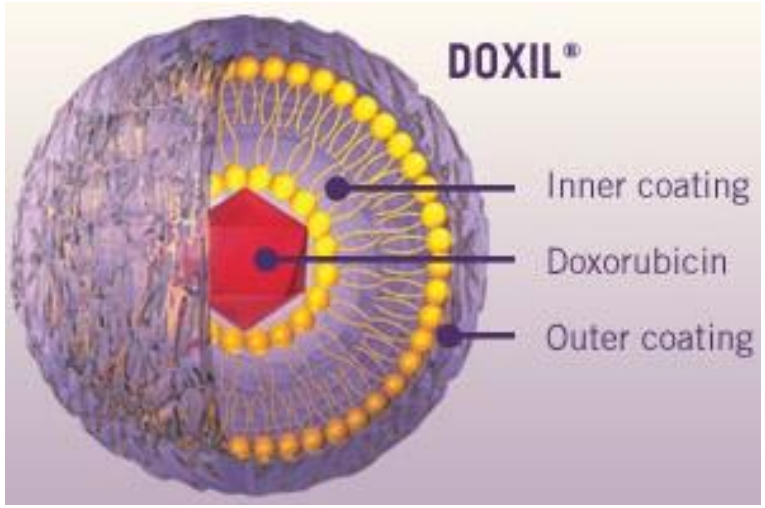


http://en.wikipedia.org/wiki/Doxorubicin

Doxil and Caelyx drugs

- It has a polyethylene glycol (PEG) coating which covers the whole cavity.

- DOXIL warnings: **„Liposomal doxorubicin may cause heart problems, including possibly fatal heart failure. Heart problems may occur during liposomal doxorubicin therapy or months to years after receiving this medication. Your risk of developing heart problems depends on your dose, medical history (including previous heart disease, radiation therapy in the chest area), and previous use of this and other drugs (including daunorubicin and cyclophosphamide). Children are at higher risk and should be monitored later in life for delayed heart problems“.**



http://www.webmd.com/drugs/drug-12120-doxil+iv.aspx

Myocet drug

- Is non-pegylated liposomal doxorubicin. It is approved in Europe and Canada for treatment of metastatic breast cancer in combination with cyclophosphamide, but is not yet approved by the FDA for use in the United States.

- Unlike Doxil (previously mentioned), the Myocet liposome does not have a polyethylene glycol (PEG) coating, and therefore does not result in the same prevalence of hand-foot syndrome.

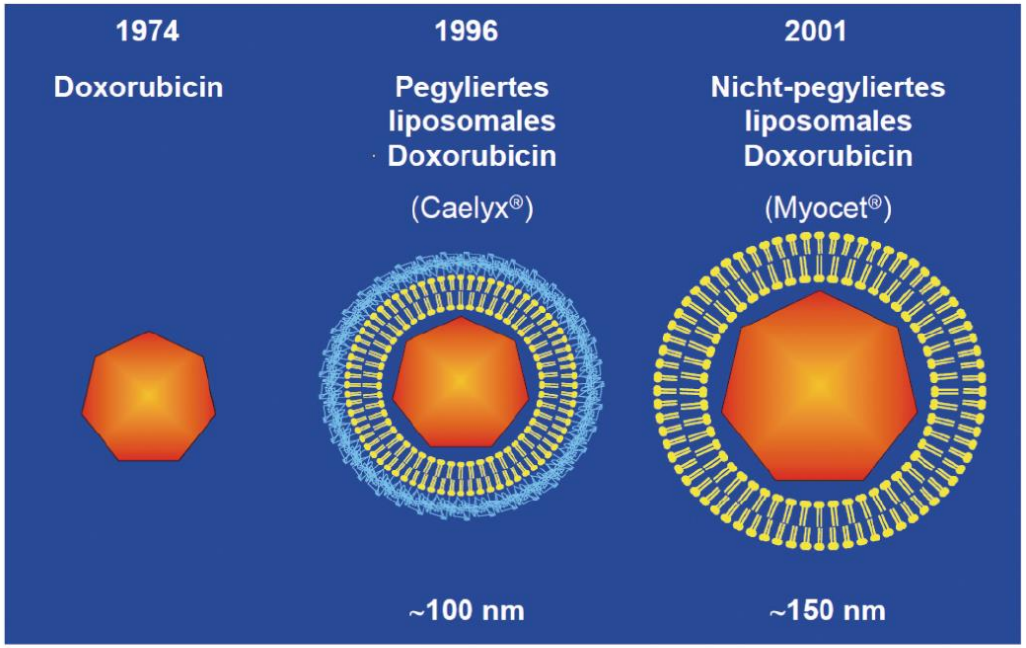
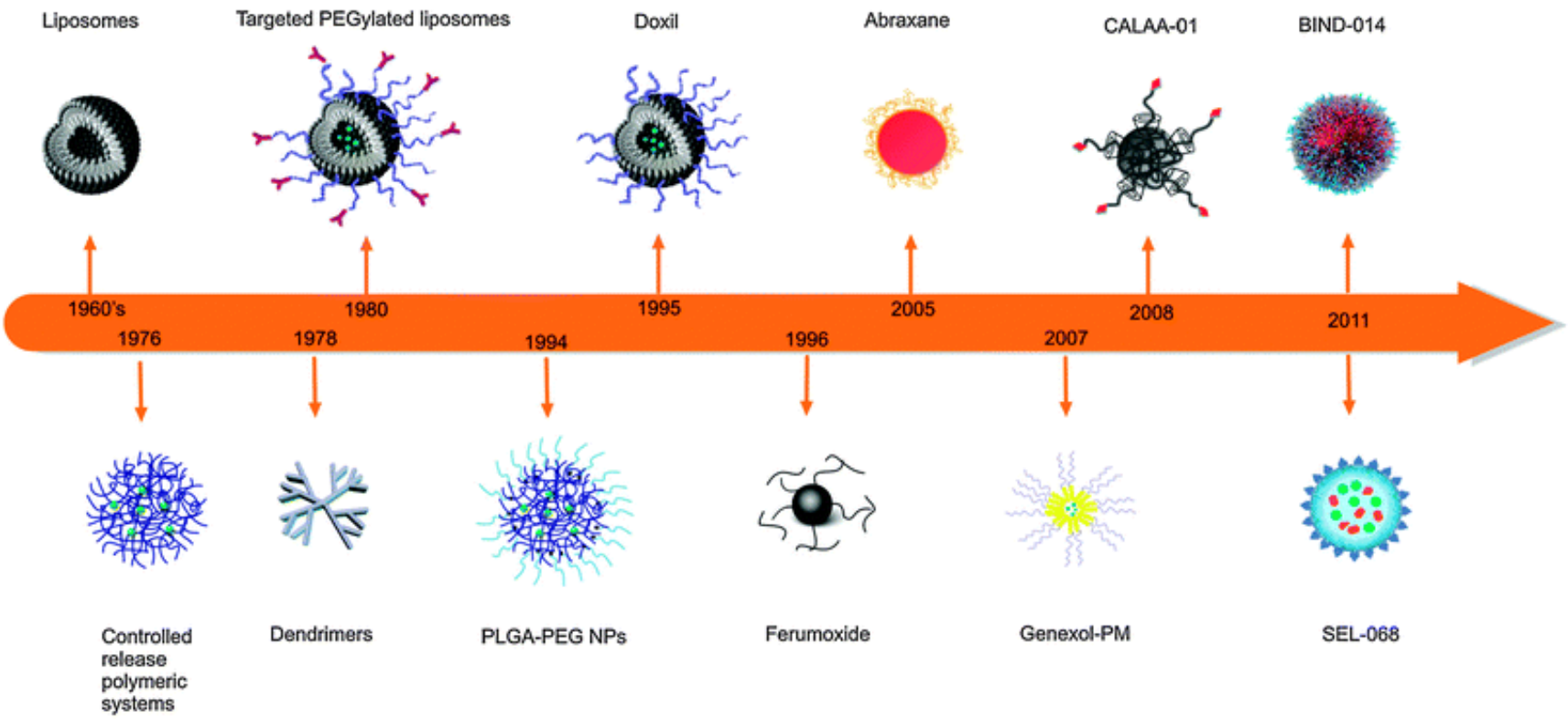


Abb. 2: Chemische Modifikation („liposomale Enkapsulierung“) von Doxorubicin

https://www.google.cz/search?q=Myocet&client=opera&hs=Ymf&channel=suggest&source=lnms&tbm=isch&sa=X

Perspectives in drug development

- The nanoparticle based drugs development in the time (Chem.Soc.Reviews.)



http://pubs.rsc.org/en/content/articlelanding/2013/cs/c3cs35431h/unauth#!divAbstract

Thank you for your attention!

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