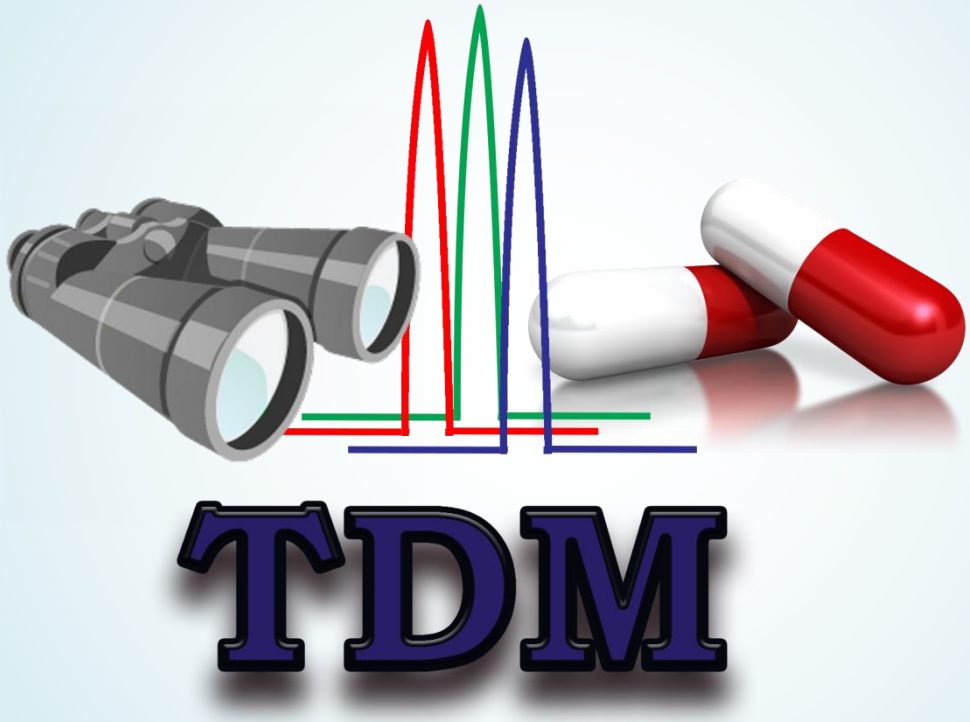
Therapeutic Drug Monitoring (TDM) in the Era of Personalized Therapy



Theodoros Karampelas,
Division of Pharmacology-Pharmacotechnology, BRFAA

Presentation Outline

1. TDM Background
2. TDM in Cancer
3. Examples of TDM applications in our lab
4. Future plans

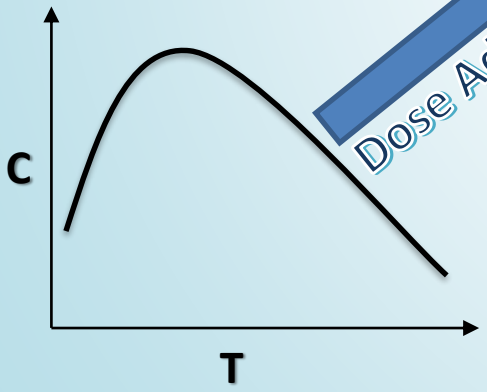
Guide to Personalized Therapy

Patient's Molecular Profile

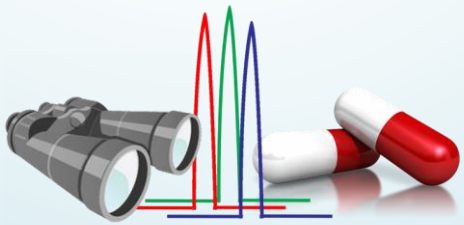
Selection of right drug

Targeted agent

Dose Adjustment



Drug Exposure



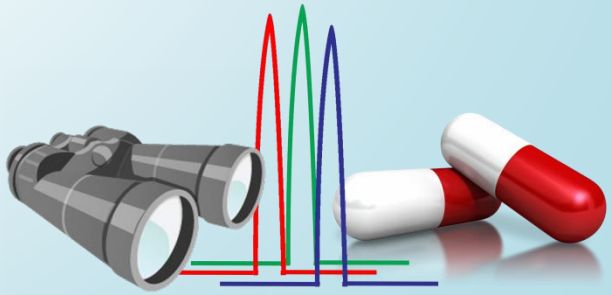
TDM

1. TDM Background

Therapeutic Drug Monitoring Definition

The measurement of the levels of a drug in a biological fluid, in order to evaluate its potential **efficacious or toxic effects** and use this information in order to optimize the drug dosage scheme and overall clinical outcome of the patient

- One of the earliest forms of personalized medicine
- Established more than 50 years ago
- Not widely implemented

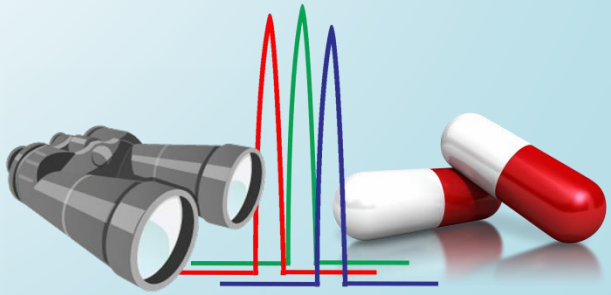


1. TDM Background

Main prerequisites of TDM:

1. A narrow therapeutic index and a wide inter-individual variability
2. A well-defined relationship between circulating levels and effect

Gao, B., Yeap, S., Clements, A., Balakrishnar, B., Wong, M., and Gurney, H. (2012). **Evidence for Therapeutic Drug Monitoring of Targeted Anticancer Therapies.** Journal of Clinical Oncology *30*, 4017–4025



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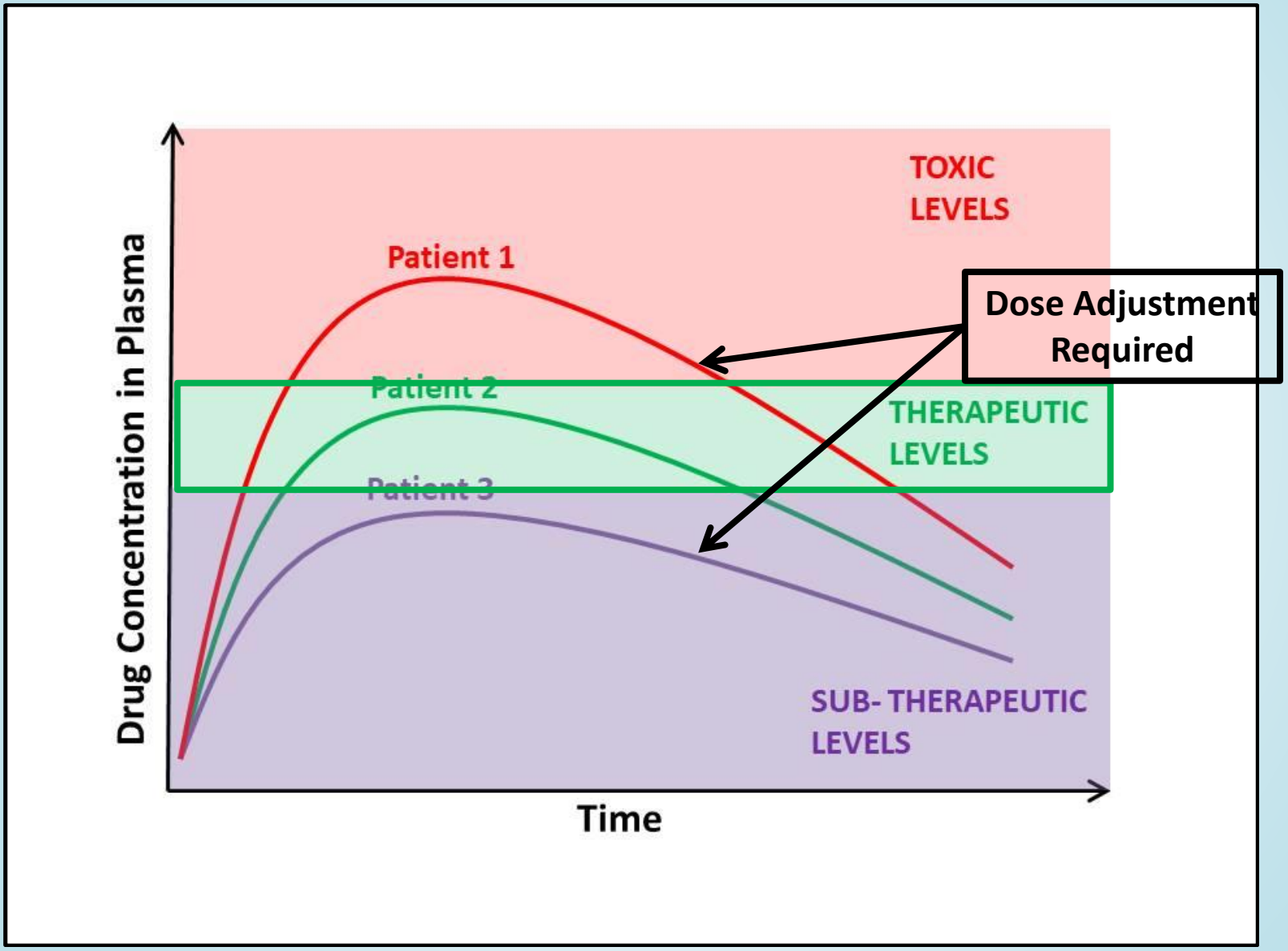
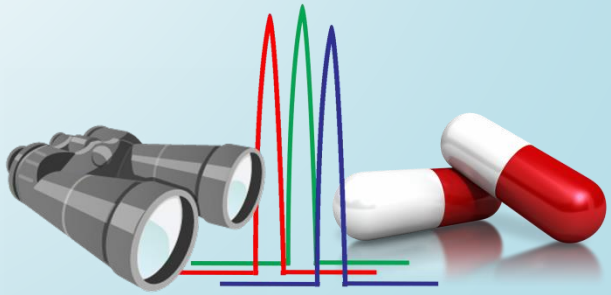


1. TDM Background

Main prerequisites of TDM:

1. A narrow therapeutic index and a wide inter-individual variability
2. A well-defined relationship between circulating levels and effect
3. Availability of reliable and clinically feasible assays



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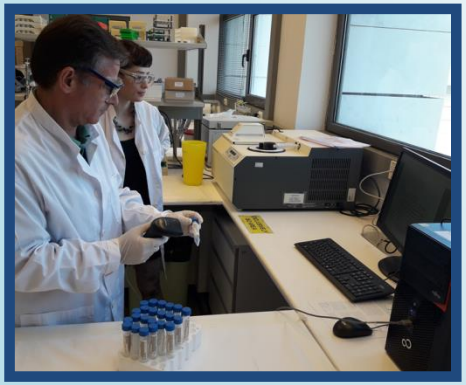
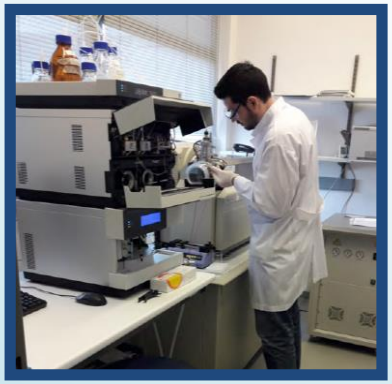
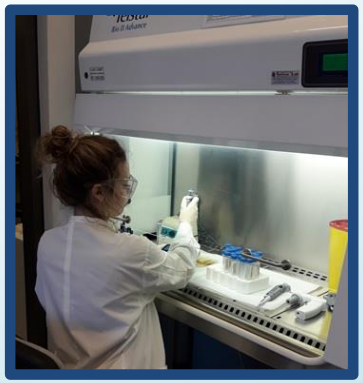
BRFAA PHARMACOLOGY

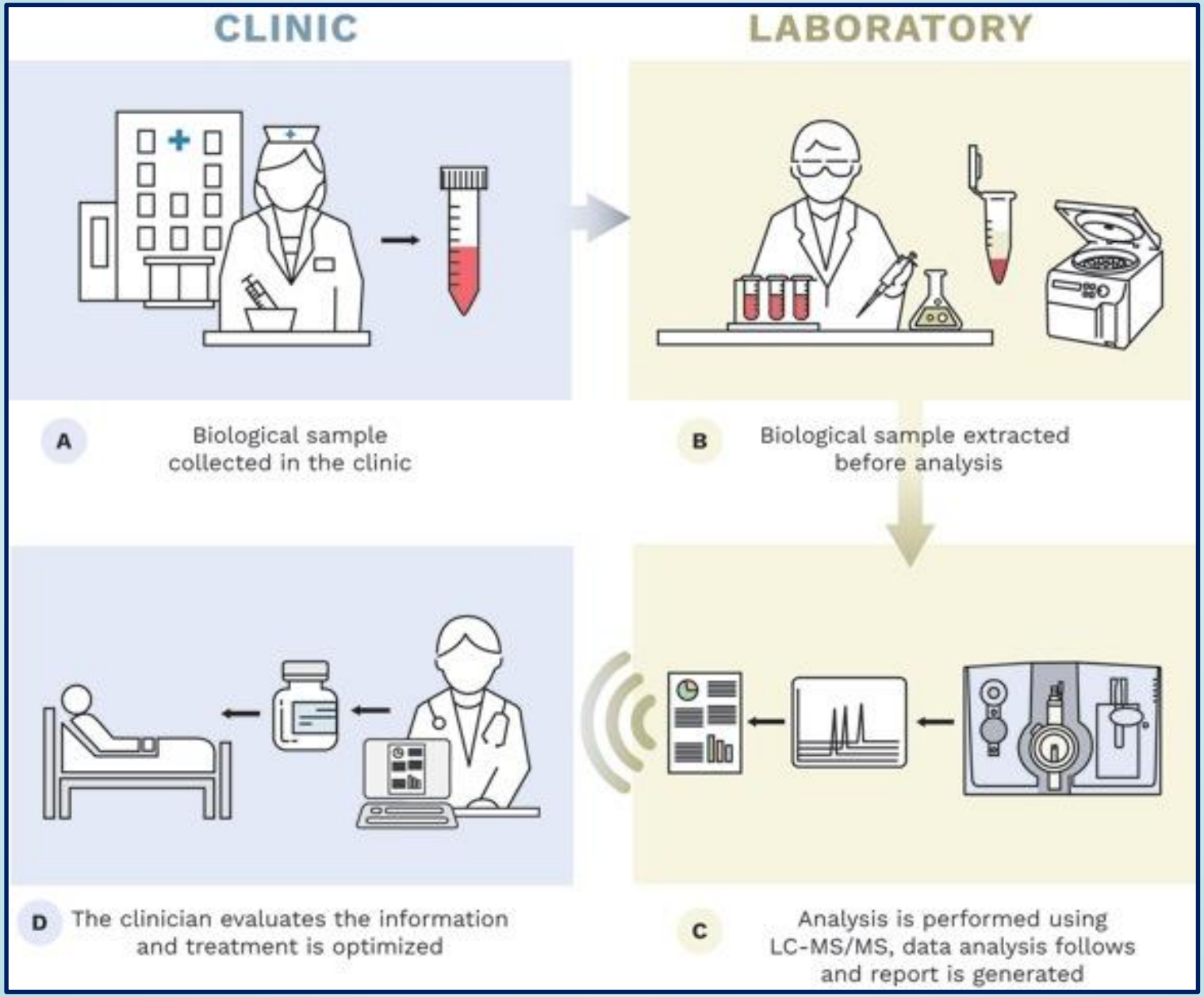
- LC-MS/MS Quantification of drugs and/or biomarkers in biological fluids (e.g. plasma, serum) derived from clinical samples
- Applicable for various types of clinical studies (Clinical studies Phase I-IV, Bioequivalence studies)
- The laboratory follows ISO17025 and GLP based procedures







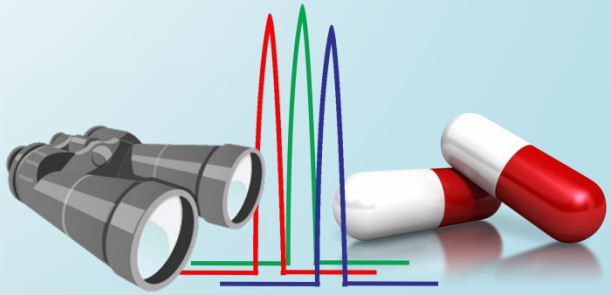
ISO 17025


CLINIC
LABORATORY
A
Biological sample collected in the clinic
B
Biological sample extracted before analysis
C
Analysis is performed using LC-MS/MS, data analysis follows and report is generated
D
The clinician evaluates the information and treatment is optimized

2. TDM in Cancer

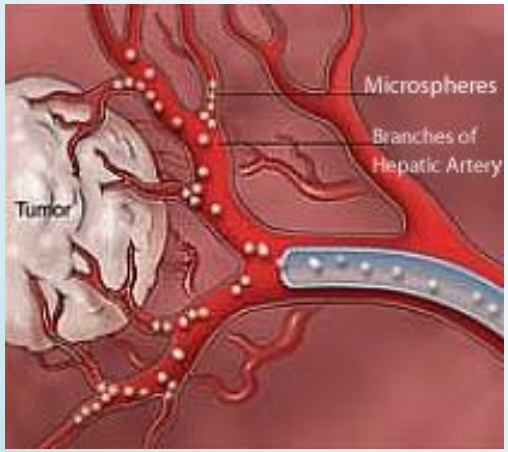
Implementation Impediments for TDM in Oncology Practice

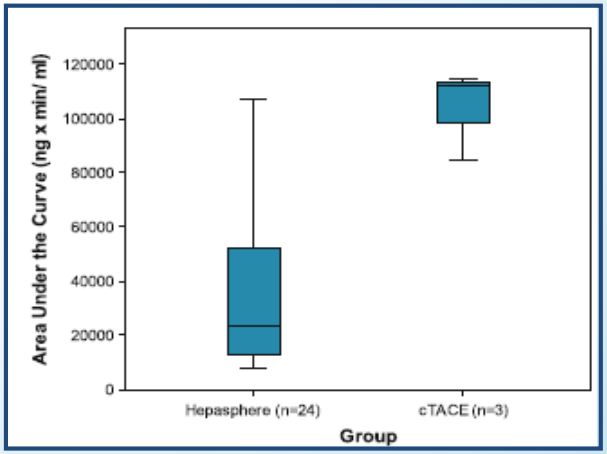
- Lack of established therapeutic ranges and concentration-effect relationships
- Frequent use of multidrug combinations with overlapping therapeutic and toxic effects
- Use of prodrugs or drugs with active metabolites
- Drugs with short elimination half-life and given by intermittent intravenous infusions



Representative Examples of TDM

Example 1: A Phase III Clinical Study for the evaluation of a new embolic material applied to patients with hepatocellular carcinoma





Example 1: Evaluation of the Pharmacokinetics of a new embolic material

Cardiovasc Intervent Radiol
DOI 10.1007/s00270-013-0777-x

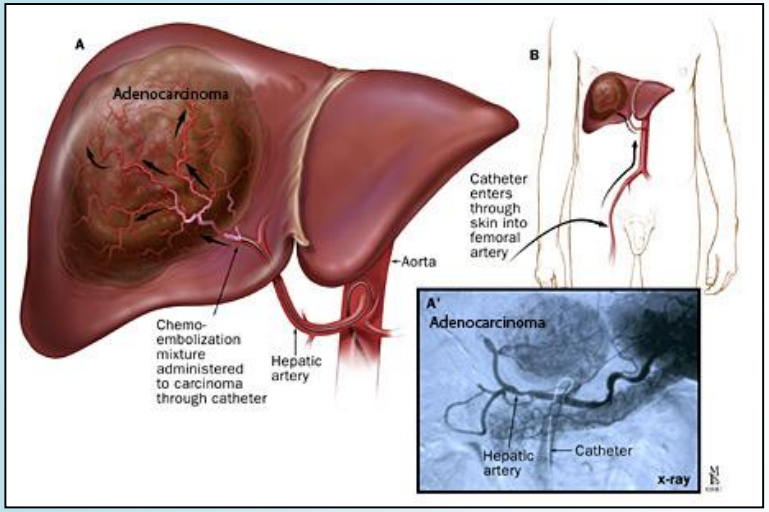
CLINICAL INVESTIGATION

Chemoembolization of Hepatocellular Carcinoma with Hepasphere 30–60 μm. Safety and Efficacy Study

Katerina Malagari · Maria Pomoni · Hippokratis Moschouris · Alexios Kelekis · Angelos Charokopakis · Evanthia Bouma · Themistoklis Spyridopoulos · Achilles Chatziioannou · Vlasios Sotirchos · Theodoros Karampelas · Constantin Tamvakopoulos · Dimitrios Filippiadis · Enangelos Karagiannis · Athanasios Marinis · John Koskinas · Dimitrios A. Kelekis

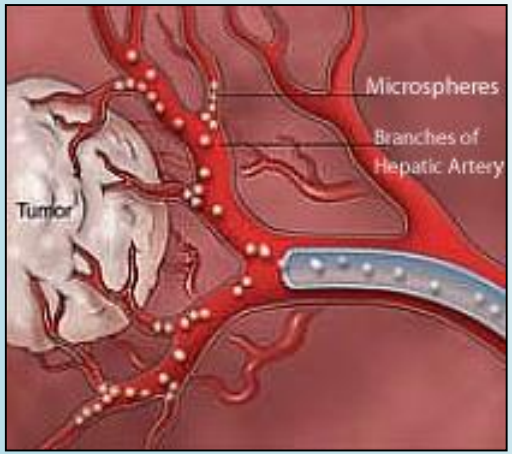
Comparison of two doxorubicin TACE administrations in HCC patients:

1. **Conventional TACE**
2. **HepaSphere microspheres TACE**



TACE

- TACE: Transcatheter Arterial ChemoEmbolization
- Administration of chemotherapy directly to the liver tumor via a catheter
- Embolization cuts off the blood supply to the tumors



TACE with microspheres

- Microspheres are biocompatible, non-resorbent and soaked in a chemotherapy agent
- Keep the chemotherapy drug in the tumor by blocking the flow to other areas
- Higher dose of the drug can be used, because less drug is able to circulate

Example 1: Evaluation of the Pharmacokinetics of a new embolic material

Doxorubicin was administered in HCC patients either with conventional or Hepasphere TACE

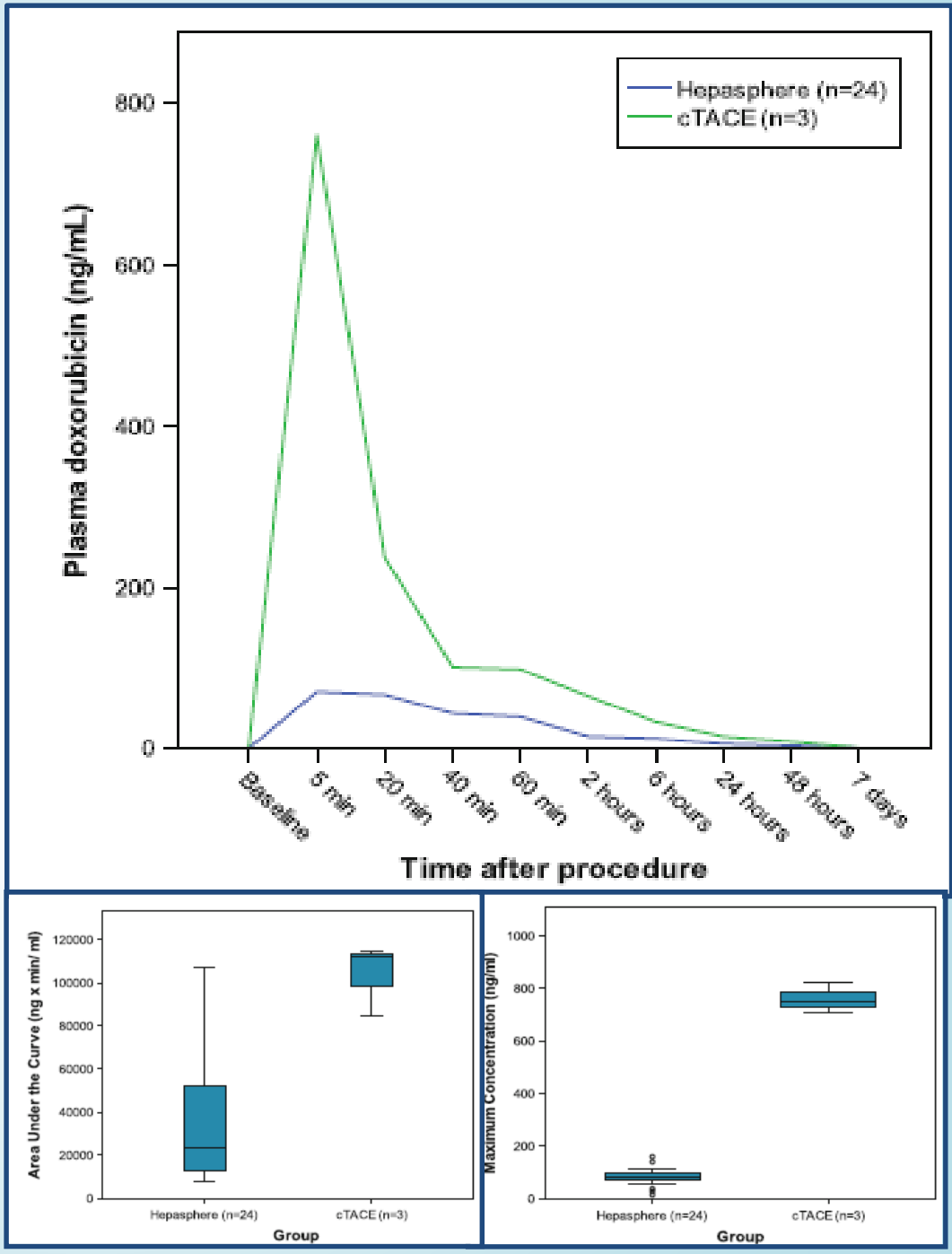
→Doxorubicin: Anthracycline antibiotic

→ Intercalates in DNA

→ Used in the treatment of many cancer types (Hematological, sarcomas, carcinomas)

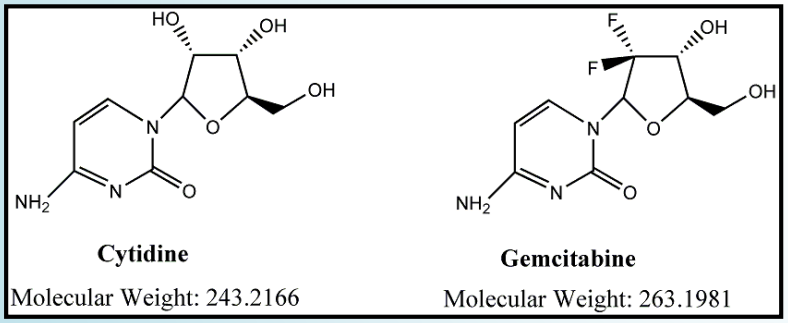
→ **HepaSphere 30–60 µm TACE showed a favorable pharmacokinetic profile against conventional TACE**

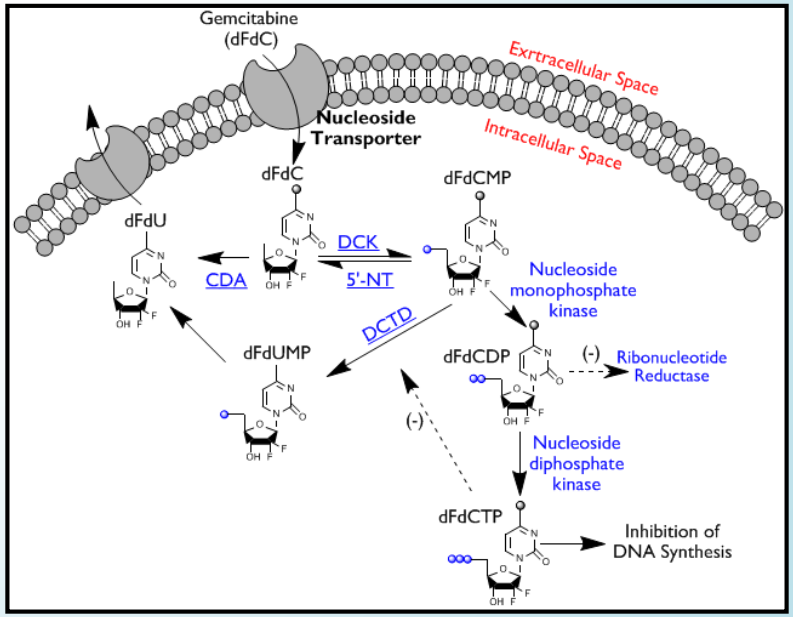
→ **Future Plan: Assess potential inverse correlation of plasma levels with efficacy**



Representative Examples of TDM

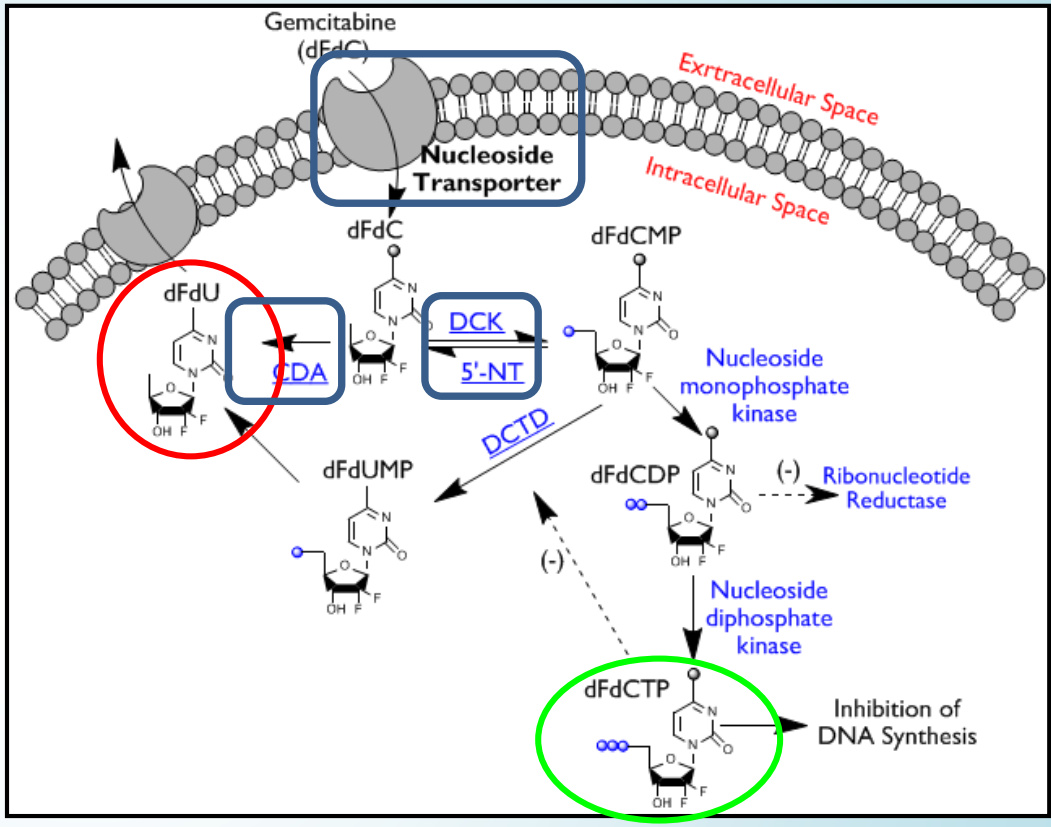
Example 2: A preclinical approach to assess the metabolic balance of gemcitabine





Gemcitabine

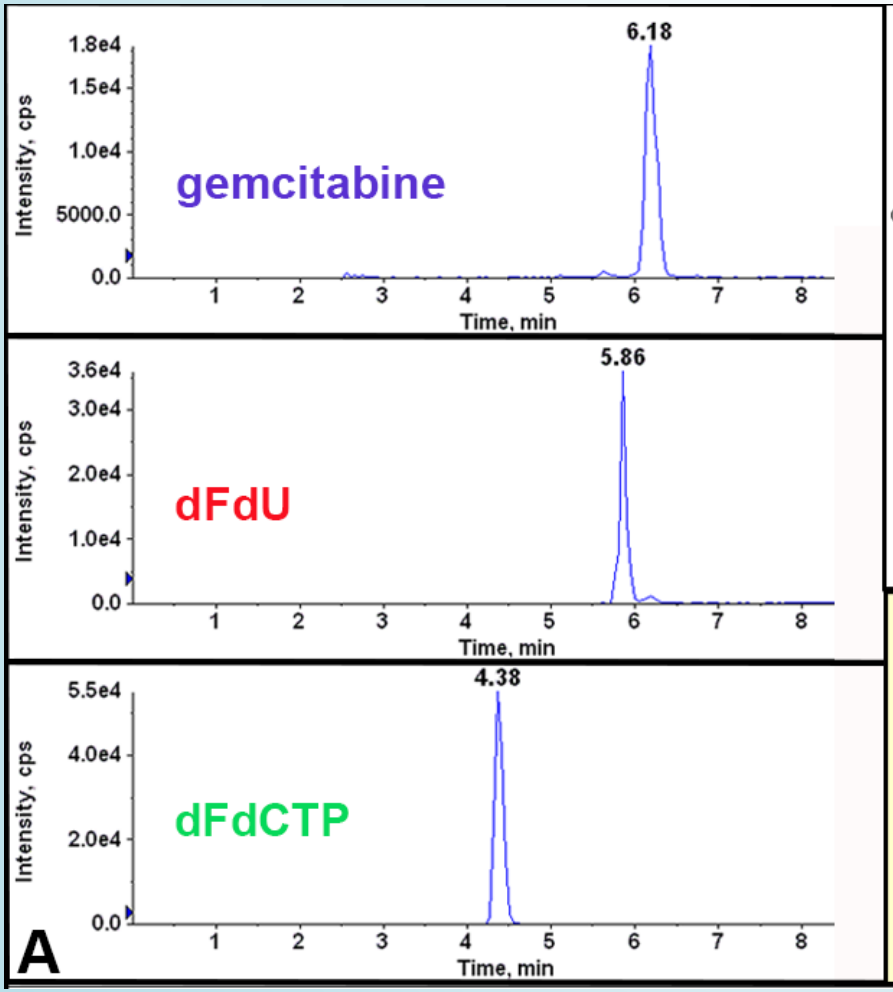
- Potent antimetabolite anticancer agent used for the treatment of several solid tumors such as colon, lung, pancreatic cancer
- Transferred into the cell by nucleoside transporters, undergoes phosphorylation and blocks DNA synthesis
- Main limitation: Rapid metabolic inactivation through deamination and formation of dFdU

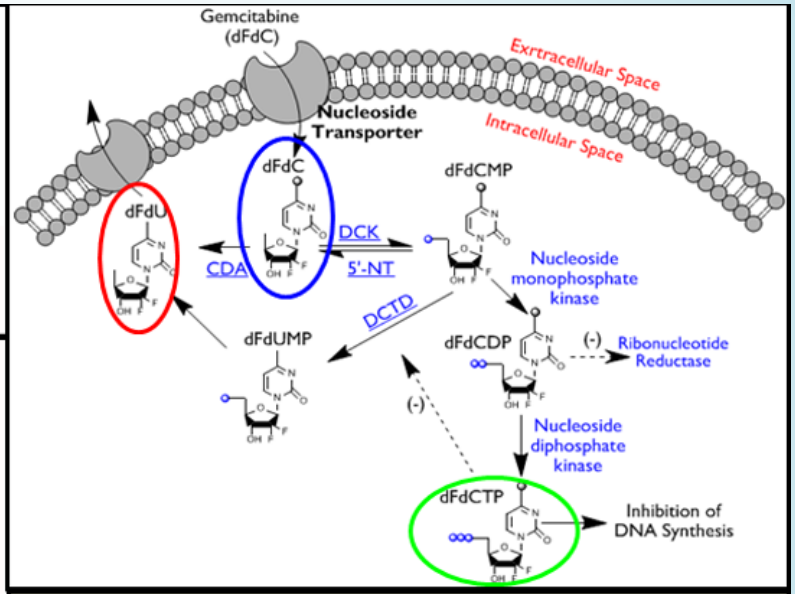


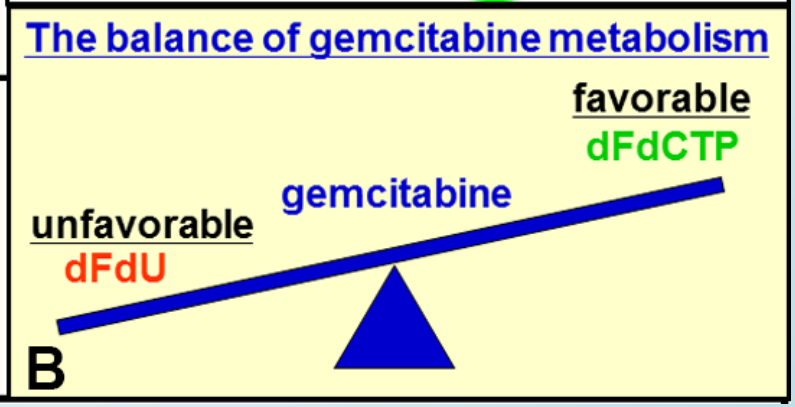
→ **Polymorphisms or mutations that are associated with induced resistance of gemcitabine metabolism enzymes could affect its efficacy**

Can MS based tools allow us to further understand/improve gemcitabine based therapies?

→ A bioanalytical methodology was developed for the identification and quantification of gemcitabine, its active (dFdCTP) and inactive metabolite

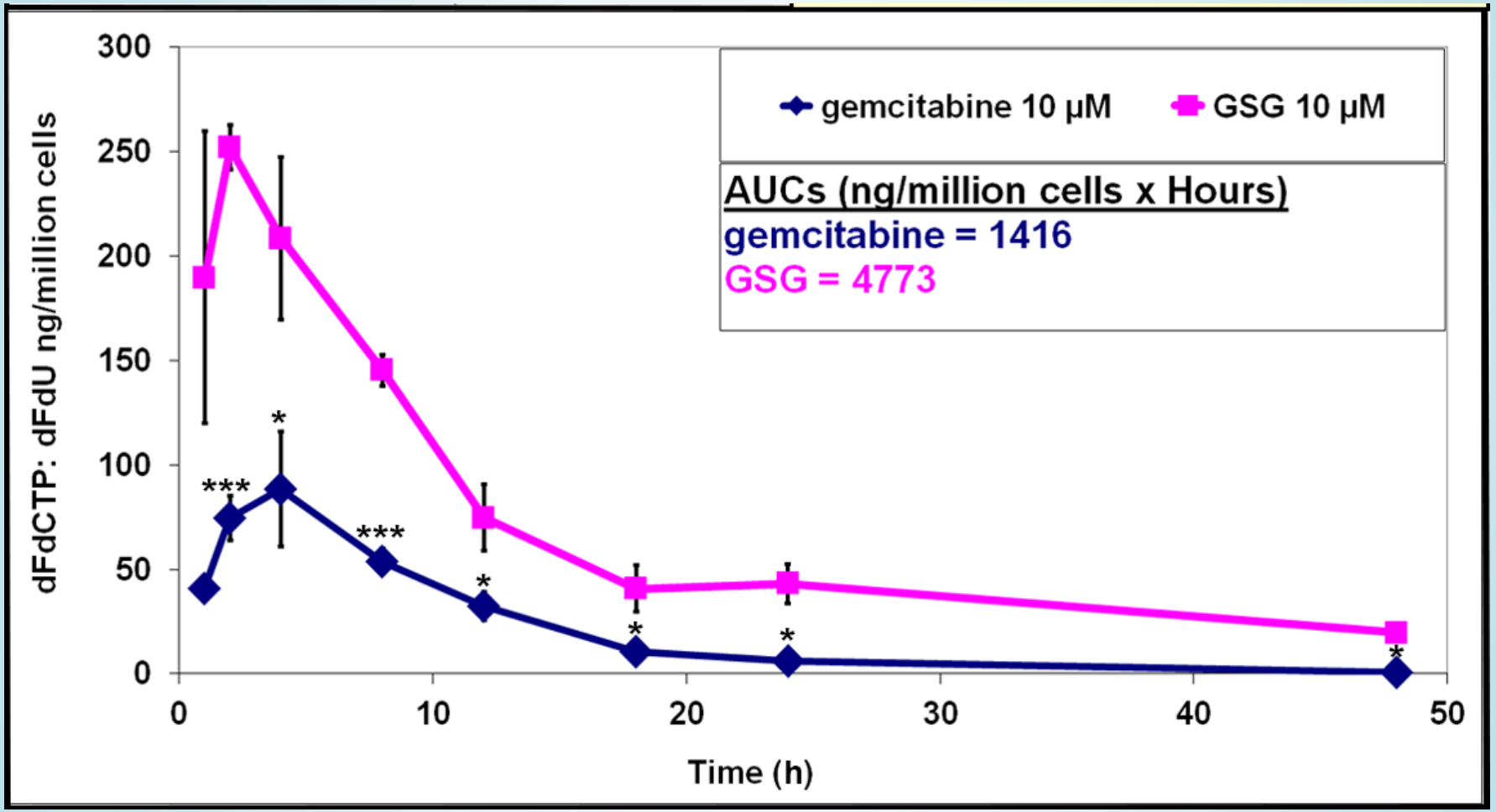






Application of the Developed Methodology on a Cell Based Assay

Evaluation of intracellular gemcitabine metabolite balance



- **Future plan: Evaluate the developed approach in clinical samples aiming to correlate gemcitabine metabolic balance with efficacy**

Future plans

- A consortium of experts on the individual specialties of TDM has been formed
- Focus on TDM in various types of cancer and cancer treatments

Clinical Protocol Preparation

(Creative Pharma Services)

Clinical Trials

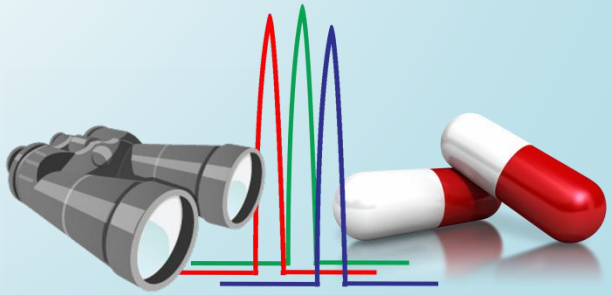
(Sotiria, "Agia Sofia" Children's Hospital, Evgenidion)

Sample Analysis

(BRFAA Pharmacology, BRFAA Proteomics)

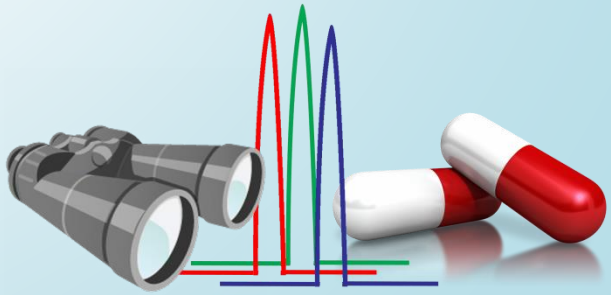
Development of an Algorithm for Dose Adjustment

(Creative Pharma Services, BRFAA, Sotiria)



Future plans

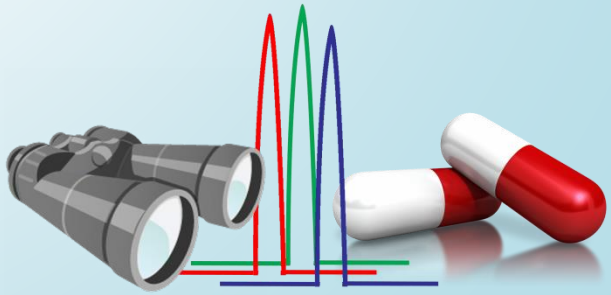
- Collaboration with ELPIDA Hospital for TDM in pediatric brain tumors
- Focus on TDM in CSF that has not been assessed in the past and might be more relevant
  - Correlation of drug levels in CSF in comparison with circulating levels
  - How radiation therapy affects the blood brain barrier (**BBB**) with respect to drug uptake
- CSF collection will not be highly interventional as patients will be carrying an Ommaya reservoir



TDM in Pediatric Brain Tumors

Molecules to be monitored in CSF

Name	Associated Disease	Matrix used from existing methodologies
temozolomide	pediatric gliomas	Plasma
methotrexate	CNS tumors	Plasma
valproic acid	CNS tumors	Plasma, Blood
carboplatin	CNS tumors	Plasma
trametinib	low grade glioma	Plasma
selumetinib	low grade glioma	Plasma, Urine



Acknowledgements

BRFAA Pharmacology

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THANK YOU!!!