Cliniques universitaires Saint-Luc

Les Jeudis de Fleurus

Perspectives for therapeutic drug monitoring

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Université catholique de Louvain, Brussels
Acorata Belgique, Fleurus, Dec 12, 2013

International Association of Therapeutic Drug Monitoring and Clinical Pharmacology

CLINIQUES UNIVERSITAIRES SAINT-LUC

What is Therapeutic Drug Monitoring?

- TDM corresponds to a multi-disciplinary service aiming to individualize/optimize drug treatment (efficacy/side effects)
- Requires excellent communication with prescribers
- Requires competencies in pharmacology/toxicology
  - Pharmacodynamics/biomarkers of activity-toxicity
  - Variations in drug disposition: pharmacokinetics/drug metabolism
  - Pharmacogenetics
- Requires competencies in drug analysis
  - Preanalytical phase
  - Analytical phase
    - Chromatographic methods/Immunoassays

Basic assumption for TDM

- Since the ’70 it was recognized that plasma drug concentrations were better related to effects than the amount of drug administered

≠

- Successful applications for digoxin, theophylline, aminoglycosides, antiepileptics, immunosuppressants…
  - Low therapeutic index, variable PK, effect difficult to quantify,…
- Largely contributes to the principles of « personalized medicine » (PK variability)
  - Identification of drug interactions
  - Identification of high or low drug clearance (accumulation)
  - Identification of non-compliance
  - …

How individualize drug treatment?
Example of immunosuppressive drugs

Adverse events
Nephro- , neurotoxicity
Hypercholesterolemia
Overimmunosuppression

Treatment efficacy
Acute rejection
Chronic rejection
Tolerance

Pharmacokinetics
Drug exposure
Drug interactions
Distribution
Metabolism
Elimination
Pharmacogenetics
(CYP3A5, P-gp,…),..

Pharmacodynamics
Action on receptors
IL2
Lymphocytes CD+4
Cylex assay
Pharmacogenetics,
Proteomic, metabolomics..

Methods
Immunoassays
LC-MSMS, RT-PCR,…
Analytical performances (specificity, sensitivity,…)
Dry spot analysis,…

What is not Therapeutic Drug Monitoring?

- TDM should not be « reduced to a simple » drug measurement from any blood specimen
  - Time-dependent concentrations
  - In absence of known expertise from the prescriber
  - In absence of accurate information allowing adequate interpretation
  - In absence of contact/dialogue with the prescriber or his staff

What are the criteria to justify TDM?

- Critical dose drugs (small therapeutic index)
  - Drugs with impredictable PK (non linear PK) or unstable pathological status (intensive care, oncology, elderly, etc…)
  - Drugs with side effects possibly misinterpreted by disease progress or symptoms
  - Absence of pharmacodynamic markers
  - Chronic treatment with risk of non compliance
- Pharmacoeconomic and cost-effective reasons
  - Shorter treatment
  - Shorter hospital stay

What drugs?

- « Old » drugs with proved interest
  - Aminoglycosides and glycopeptides (gentamicin, vancomycin..)
  - Cardiac glycosides (digoxin)
  - Antiepileptics (carbamazepine, valproic acid, phenytoin..)
  - Methotrexate
  - Theophylline
  - Immunosuppressive drugs (cyclosporine, tacrolimus, everolimus, sirolimus, MPA..)
  - Some antiarrhythmic agents (amiodarone)
  - Some antidepressive agents (Lithium, TCA ?)

What drugs?

- « New » drugs of interest
  - Newer antiepileptics (levetiracetam, oxcarbazepine, lamotrigine..)
  - Some antiretrovirals (efavirenz, lopinavir,..)
  - Some cephalosporins (cefepime, meropenem..)
  - Some antifungals (posaconazole, itraconazole, voriconazole..)
  - Some cytotoxic agents (imatinib, irinotecan, tamoxifen, L-asparaginase, ..)
- Drugs with limited interest (?)
  - Benzodiazepines
  - SSRI

TDM challenges and issues

- But…limitations of TDM
  - Sometimes poor relationship between trough drug concentration (C_0) and clinical outcome
  - High dependency of sampling time accuracy
    - Difficulty to get reliable data from nursing (times, dose, interval,…)
- Difficulty to get real consensus for therapeutic ranges
  - Maybe as a consequence of erratic blood sampling, variable analytical methods,…
- As a consequence: limited and still debated success in some applications
  - Mycophenolate, antiretrovirals, cytotoxics, antidepressants,…

TDM: search for better PK-PD markers the « quest of the GRAAL »

- Since the years ’70, permanent search for optimal marker of efficacy/toxicity e.g.:
  - Plasma, whole blood, free vs total fraction
  - Bioassay (MLC, RRA, EA, MIC,…),
  - Sampling time: C_0, C_2, C_{max}, full AUC …
- Single blood sampling: easy but sometimes weak for predicting effects (e.g. C_0,…)
  - Pharmacokinetic reasons
    - Drug ≠ endogenous analyte (e.g. creatinine)
    - Logistic issues (accuracy in routine setting)
    - Sometimes lack of good relationship between C_0 and AUC
  - Pharmacological reasons
    - Concentration- or time-related effects e.g. antibiotics
    - Blood conc not well related to target (intra-cellular) site conc,...

Evolution in Laboratory Medicine

- Important economic pressure and progress in technology
- Trend to « industrialize » laboratory testing
  - Increased automation
  - Consolidation, laboratories merging
  - Reduction of test production costs
- Need to increase the Medical expertise and the « value-added » for any laboratory tests
  - Need to optimize the value of any laboratory result
  - Knowledge service
  - Better interpretation
  - Guidance in prescription
  - Evidence based …

How could progress TDM during the coming decade?

Three main perspectives

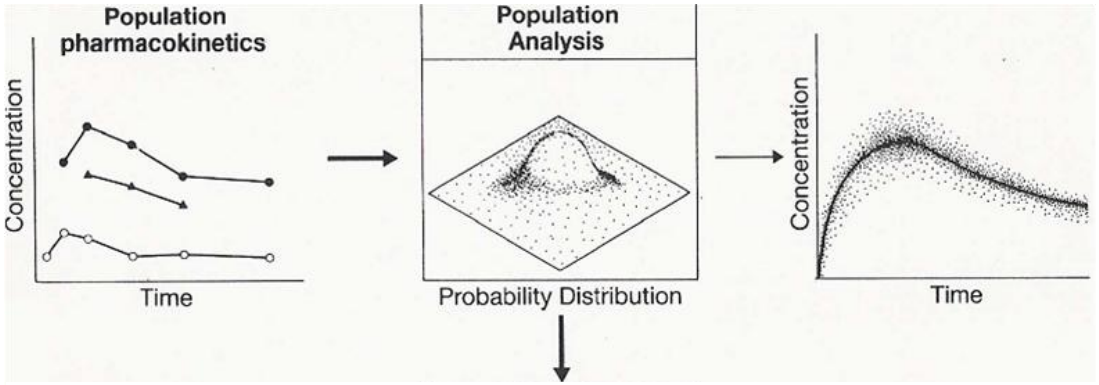
First perspective of progress
Pharmacology:
Strengthening of the PK-PD relationship

Stronger pharmacokinetics involvement

- Better relationship between AUC and drug effects than C_0
- Direct access: possible but difficult
  - 8-12 blood sampling
  - Medical issue, costs, time,…
- Indirect access: prediction through mathematical approaches
  - Limited sampling strategies: 2-3 blood samples with equations to specific populations: (need strict sampling times)
  - Population pharmacokinetics with Bayesian estimates: (allow more flexibility in sampling times)
- Need standardization of TDM approaches (cfr P Marquet)

Drug Area Under the time-concentration Curve (AUC)

Population pharmacokinetics modelling with optimal sampling strategy for Bayesian estimation

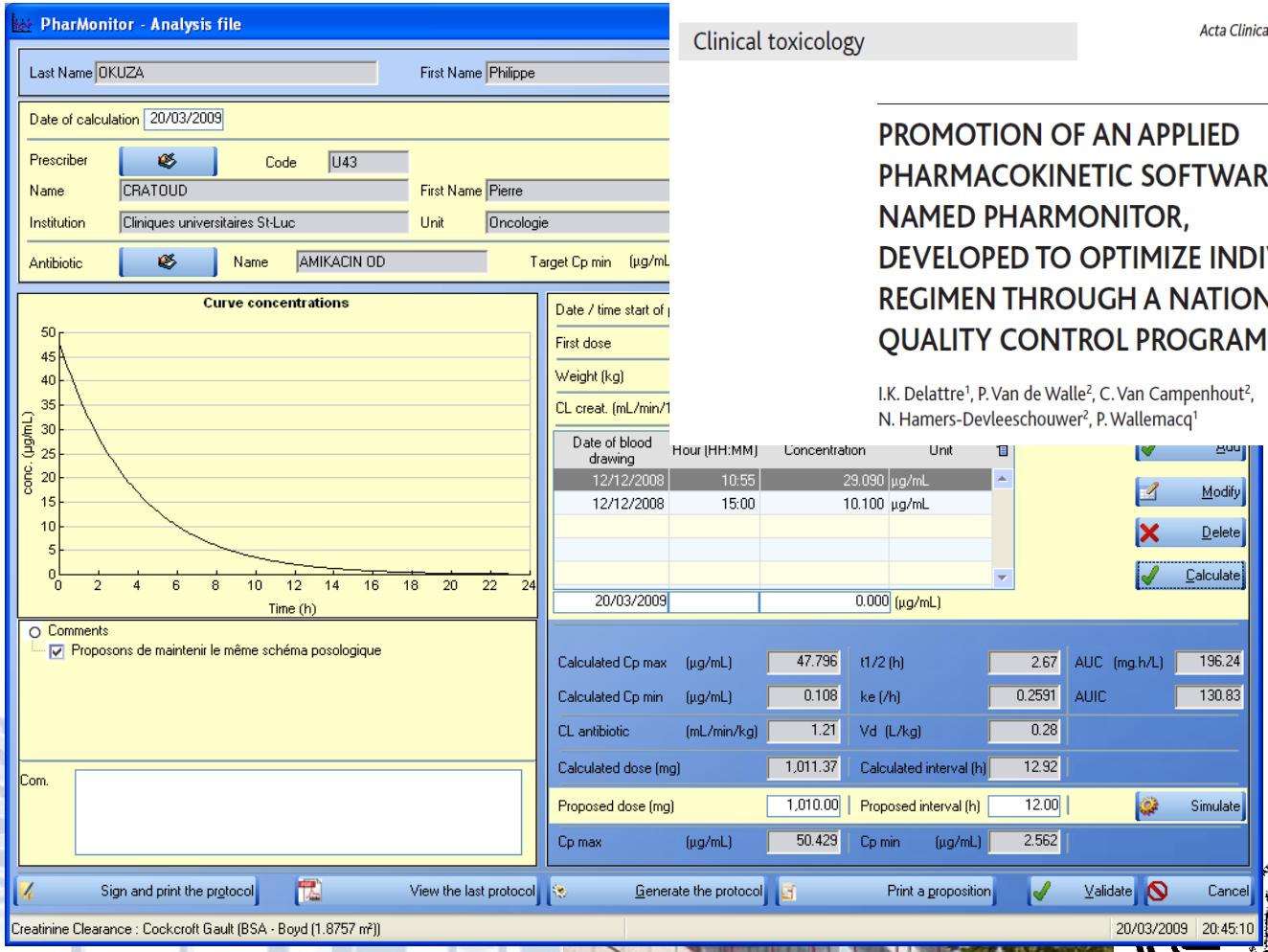


ORIGINAL RESEARCH ARTICLE
Clin Pharmacokinet 2009; 48 (11): 745-758
0312-5963/09/0011-0745/$49.95/0

Limited Sampling Models and Bayesian Estimation for Mycophenolic Acid Area under the Curve Prediction in Stable Renal Transplant Patients Co-Medicated with Ciclosporin or Sirolimus

Flora T. Musuamba,[1] Annick Rousseau,[2] Jean-Louis Bosmans,[3] Jean-Jacques Senessael,[4] Jean Cumps,[1] Pierre Marquet,[2] Pierre Wallemacq[5] and Roger K. Verbeeck[1]

Drug Area Under the time-concentration Curve (AUC)



Clinical toxicology

Acta Clinica Belgica, 2010; 65-Supplement 1

PROMOTION OF AN APPLIED PHARMACOKINETIC SOFTWARE, NAMED PHARMONITOR, DEVELOPED TO OPTIMIZE INDIVIDUAL DOSAGE REGIMEN THROUGH A NATIONAL QUALITY CONTROL PROGRAM

I.K. Delattre[1], P. Van de Walle[2], C. Van Campenhout[2], N. Hamers-Devleeschouwer[2], P. Wallemacq[1]

Access portal to the websites of routine and clinical trials of the Limoges University Hospital laboratory of Pharmacology

CHU Centre hospitalier universitaire Limoges

VeriSign Secured

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

French version

English version

Access | TDM - Modalities | Available tools | ISBA Newsletters | Publications

Please identify yourself

Login :

Password :

You lost your identifier and/or your password

Delete | Enter the Websites

Registration on ISBA website

Pharmacodynamic biomarkers

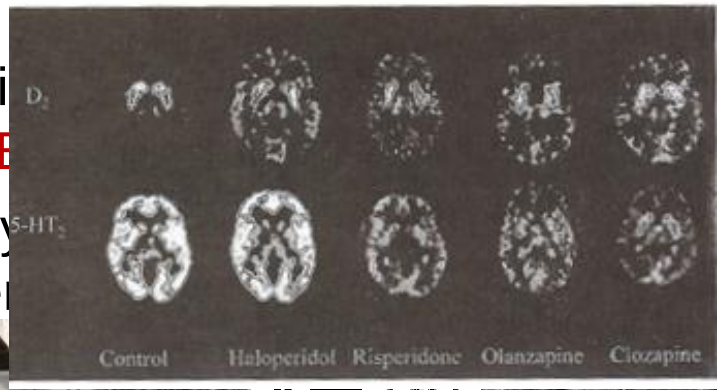
- Two patients exposed to similar drug blood conc may respond differently!
  - Possible different receptor-effector response
  - Individual susceptibility (genetics, environment, …)
- Urgent need to add PD biomarkers in the TDM activity
  - More difficult to implement routinely
  - Lack of automation
  - Lack of well identified PD biomakers
  - Lack of quality controls and proficiency scheme
  - Lack of standarization, etc…
- Proteomics, metabolomics…

Pharmacodynamic biomarkers

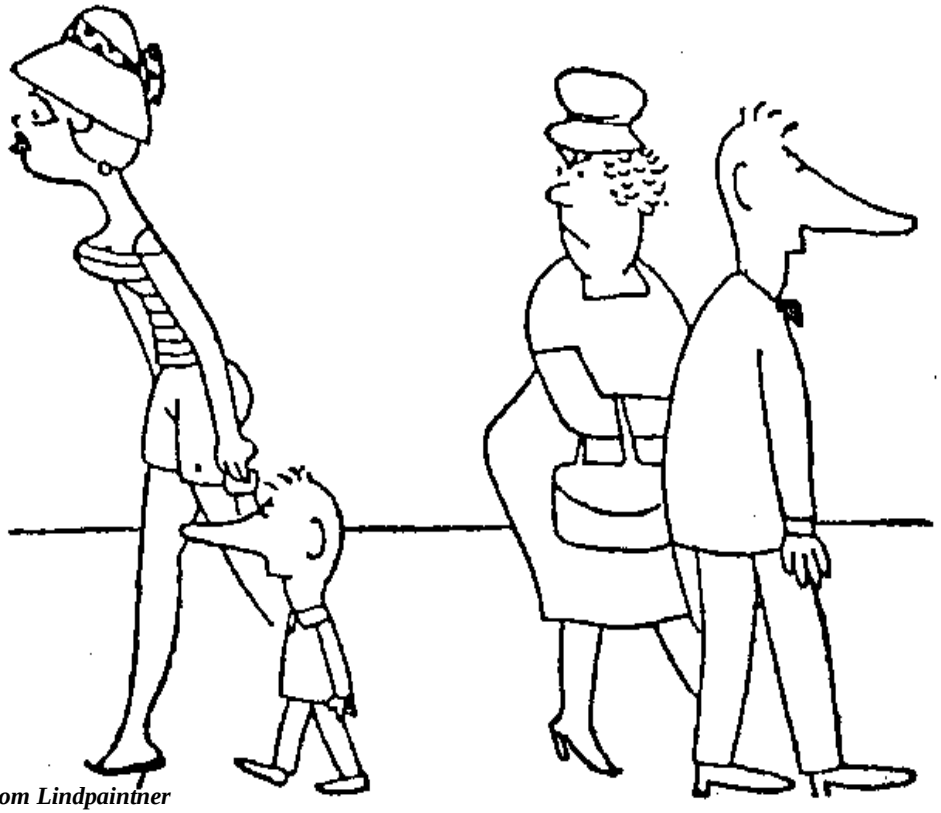
- Antibiotics:
  - MIC, peak/MIC, Time above MIC, AUIC…
- Immunosuppressants
  - Lymphocytes proliferation (Proliferating Cell Nuclear Antigen)
  - Expression of surface antigens of T-cell
  - IFN- γ ELISPOT assay
  - Quantification of intracell IL-2 in CD8+T cells
  - Measure of the ATP production from stimulated T-cells (Cylex ImmuKnow assay)
  - Specific enzymes activity (IMPDH, calcineurin,…)
- Antiretrovirals
  - Viral load,
  - CD4,
  - RNA-HIV,…

Pharmacodynamic biomarkers

- Antidepressive agents
  - Difficulty in defining the efficacy (scoring) of psychoactive drugs
  - Existence of standardized clinical rating scales to evaluate therapeutic responses and SE
    - To assess efficacy: Brief Psychiatric Rating Scale (BPRS)
    - Positive and Negative Symptom Scale for Schizophrenia (PANSS)
    - To assess extrapyramidal SE: Abnormal Involuntary Movement Scale
- Antipsychotic agents
  - Dosage titration to a target % of dopami
    by tomography (Positron Emission or PE
  - Therapeutic effect but also SE of antipsy
    blockade of D_2 receptors for schizophre



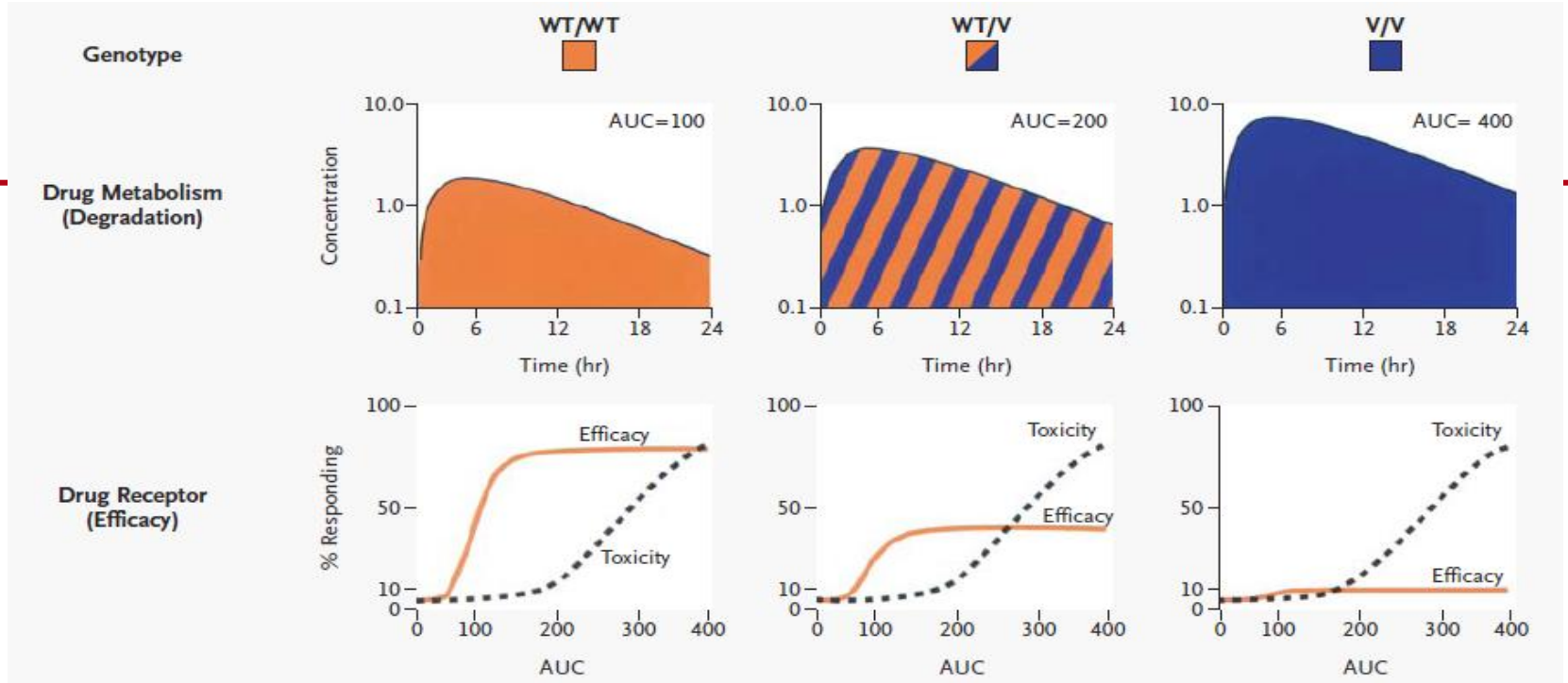
Genetic factors



Adapted from Lindpaintner

Pharmacogenetics

- Genetics polymorphisms may affect both
  - The drug disposition (e.g. transport proteins, CYP3A5, CYP2D6, etc…)
  - The receptor activity (e.g. IMPDH, BCR-ABL kinase activity,…)
- More pharmacogenetic-based recommendations at the onset of a treatment will appear
  - To select drugs
  - To adjust doses



Metabolism genotype		Receptor genotype	Response: Efficacy	Response: Toxicity
Polygenic Drug Response				
WT/WT	+	WT/WT	65%	Low (5%)
WT/WT	+	WT/V	32%	Low
WT/WT	+	V/V	9%	Low
WT/V	+	WT/WT	79%	Moderate (15%)
WT/V	+	WT/V	40%	Moderate
WT/V	+	V/V	10%	Moderate
V/V	+	WT/WT	80%	High (80%)
V/V	+	WT/V	40%	High
V/V	+	V/V	10%	High

Pharmacogenetics

American Journal of Transplantation 2006; 6: 2706–2713
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2006.01518.x

CYP3A5 and *ABCB1* Polymorphisms and Tacrolimus Pharmacokinetics in Renal Transplant Candidates: Guidelines from an Experimental Study

V. Haufroid[a,b,*], P. Wallemacq[b], V. VanKerckhove[a], L. Elens[a], M. De Meyer[c], D. C. Eddour[c], J. Malaise[c], D. Lison[a] and M. Mourad[c]

Introduction

Tacrolimus (Tac, FK506) is widely used to prevent acute rejection following solid-organ transplantation. Like cyclosporin (CsA), this drug is characterized by a narrow

Intracellular drug concentrations

- A similar « postulate » could be used
  - Dosis vs plasma (blood) concentration (rationale for classical TDM)
    - Blood pharmacokinetics, -genetics
  - Plasma (blood) concentration vs target intracellular concentration
    - Cellular pharmacokinetics, -genetics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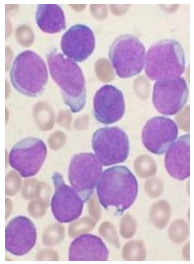
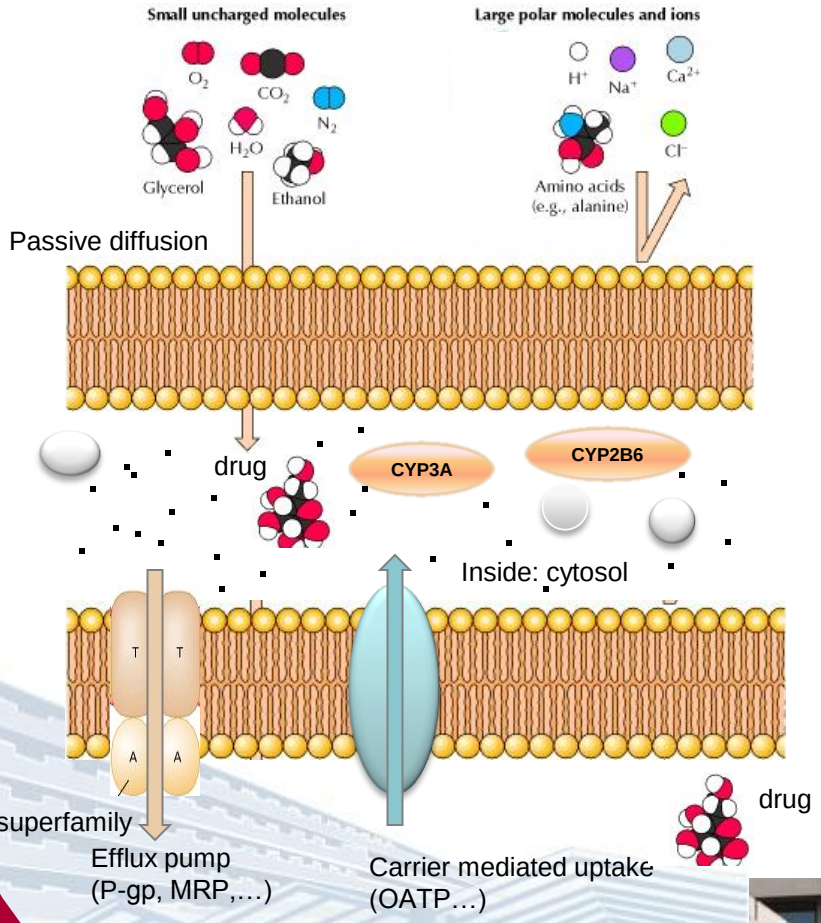


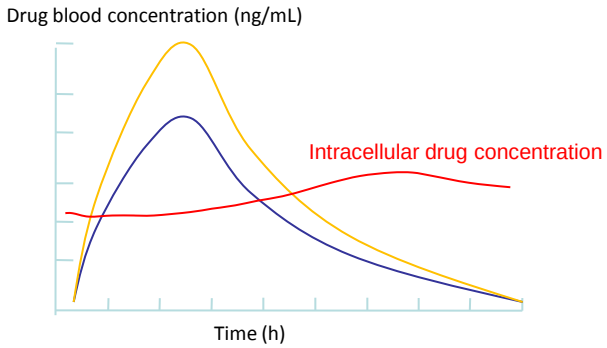
- First reports for the interest of intracellular drug conc.
  - Hepatocytes (Liver Tx) CsA in 1992 (Sandborn et al, Hepatology 1992, 15,1086-91)
  - Lymphocytes CsA in 1998 (Masri et al, Transplant Proc, 1998,30,3561-2)
  - Lymphocytes Lamivudine in 1999 (Moore et al, AIDS, 1999, 13,2239-50)
  - Lymphocytes Protease inhibitors in 2002 (Chaillou S, HIV Clin trials, 2002,3,493-501)
  - PBMC MPA in 2007 (Benech H, J Chromatogr B Analyt Technol Biomed Life Sci, 2007,853,168-74)

Intracellular drug concentration

- Intracellular drug concentrations are regulated by passive or active processes
  - Blood or plasma free conc
  - Physicochemical factors across bilayer membranes (mw, pKa, logP)
  - Carrier-mediated transport (efflux or influx pumps,…)
  - Local biotransformation (CYP)
- Cellular specific PK and PG
- Ratio blood vs intracellular concentration not constant

Intracellular drug concentration



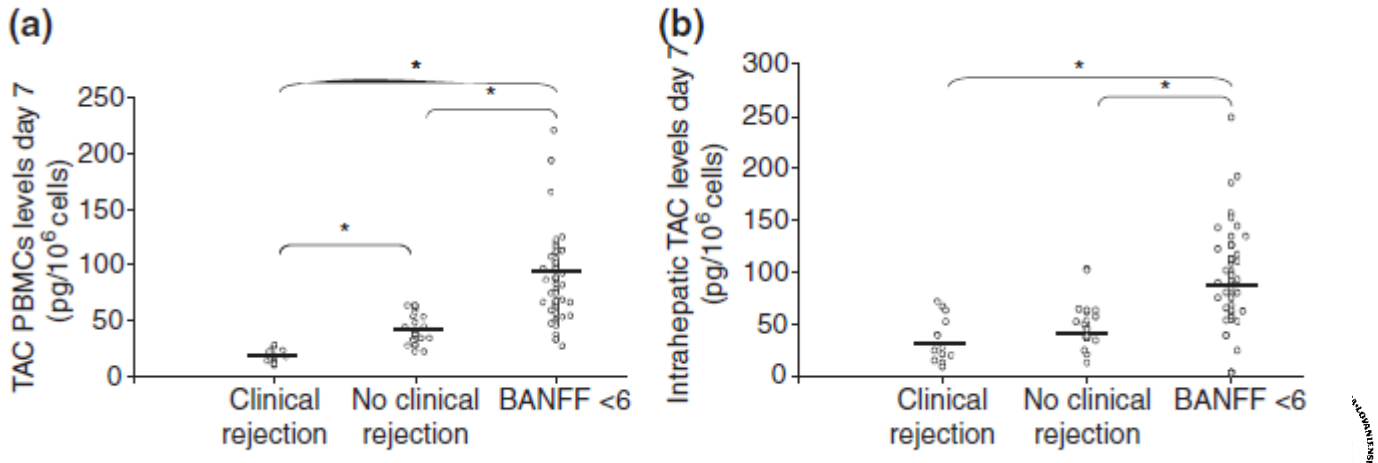


Intracellular drug concentration

ORIGINAL ARTICLE Transplant International © 2011 European Society for Organ Transplantation **25** (2012) 41–47

Correlation of tacrolimus levels in peripheral blood mononuclear cells with histological staging of rejection after liver transplantation: preliminary results of a prospective study

Arnaud Capron,[1,2] Jan Lerut,[3] Dominique Latinne,[4] Jacques Rahier,[5] Vincent Haufroid[1,2] and Pierre Wallemacq[1,2]



Second perspective of progress: Analytical aspects

Analytical methods improvement

- Clinicians need consistent results
- 20-50% variations among methods should not be accepted anymore
- Need of international standarization supported by a consortium of clinical labs, scientific associations, industries and health authorities
  - To limit calibration bias occuring both with IA and LC-MSMS
  - To limit interferences with endogenous compounds or metabolites
  - To improve outcome studies comparison
- Increase sensitivity adapted to clinical needs

Analytical methods improvement and standardization

- Need to improve automation and robustness of IA and LC-MSMS
  - Automated preanalytical phase (both IA and LC-MSMS)
  - Reduce heterophilic antibodies interferences (IA)
  - Reduce risk for ion suppression effect (LC-MSMS)
  - LC-MSMS perspectives of progress
    - Not yet fully adapted to routine laboratory medicine
    - Lack of automation (e.g. User friendly software, on-line extraction, random access, bare codes...)
    - Lack of comprehensive and rapid support from MS manufacturer's (24h hotline) as compared to major diagnostic companies

Emergence of immunosensors
« Real-time drug measurements »

- Possible for hospitalized patient to determine individual PK and dosing
- Blood drawn (< 1 µL) by intravenous microdialysis catheter (MicroEye®)
- Miniaturisation down to micro- or nanoscale
- Short intervals of measurements (e.g. few min)
- Detection by optical chip (nanotechnology) through luminescent signals

Project FP7, NANODEM 2010
F Baldini et al.

Emergence of immunosensors
« Real-time drug measurements »

- Direct online (e.g. 48 h) with individual PK and AUC measurements of the drug free fraction
  - Real-time full AUC (> 500 measurements)
- Very sensitive
- Multiplexing measurements possible

Emergence of immunosensors
« Real-time drug measurements »

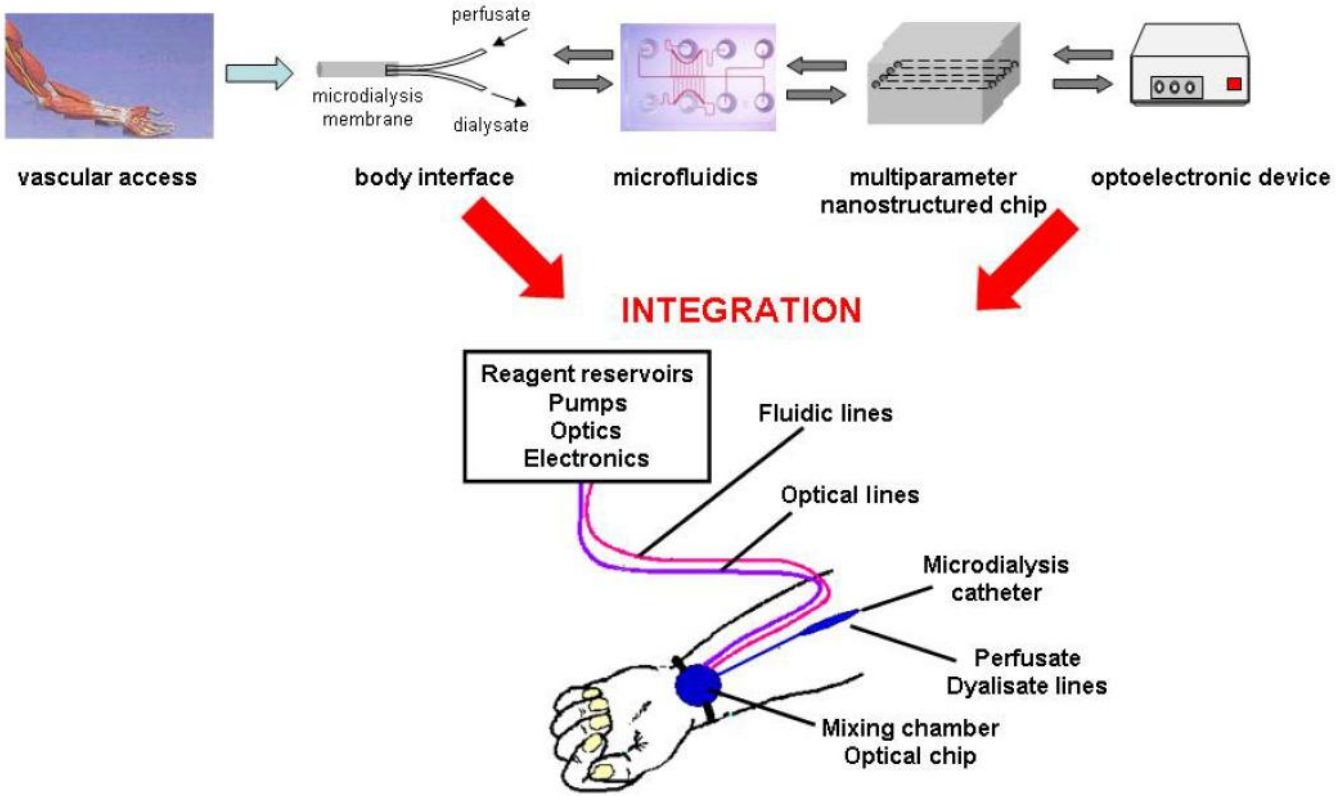


Figure 1. Diagram of the proposed POCT device.

Project FP7, NANODEM 2010
F Baldini et al.

Luminescent-based optical sensors

- Biochip considered as an array of biosensors (multiple analyses)
- Use of polymeric or silica nanoparticles carrying fluorophores
- Use of magnetic nanoparticles to concentrate the analyte in the sensing chip
- Possibility of large scale automation and re-use (low costs)
- Fluorescent scanners used for lecture

Project FP7, NANODEM 2010
F Baldini et al.

Optical sensors

Biosensors and Bioelectronics 26 (2011) 4423–4428

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios

Direct surface plasmon resonance immunosensor for *in situ* detection of benzoylecgonine, the major cocaine metabolite

Eva M. Munoz[a], Silvia Lorenzo-Abalde[b], África González-Fernández[c], Oscar Quintela[d,1], Manuel Lopez-Rivadulla[d], Ricardo Riguera[a,*]

[a] Department of Organic Chemistry and Centre for Research in Biological Chemistry and Molecular Materials (CIQUS), University of Santiago de Compostela, Av de las Ciencias, 15782 Santiago de Compostela, Spain
[b] Cienytech (Cientisol, SL), Rúa Xosé Chao Rego, 10 Bajo, 15705 Santiago de Compostela, Spain
[c] Immunology, Biomedical Research Centre (CINBIO), University of Vigo, 36310 Vigo, Spain
[d] Forensic Toxicology Service, Institute of Legal Medicine, University of Santiago de Compostela, 15782 Santiago de Compostela, Spain

- *In situ*
- Real time monitoring
- Oral fluid
- High sensitivity (< 4 ng/mL)
- (SAMHSA oral fluid cutoff: 20 ng/mL)
- Reusable test

Anal Bioanal Chem (2012) 402:109–116
DOI 10.1007/s00216-011-5492-3

TRENDS

Optical fibre gratings as tools for chemical and biochemical sensing

F. Baldini · M. Brenci · F. Chiavaioli · A. Giannetti · C. Trono

- Label-free
- *In situ*
- Real time

Optical sensors

Anal Bioanal Chem (2011) 401:2301–2305
DOI 10.1007/s00216-011-5304-9

TECHNICAL NOTE

A clinical trial for therapeutic drug monitoring using microchip-based fluorescence polarization immunoassay

Tomoya Tachi · Tetsunari Hase · Yukihiro Okamoto · Noritada Kaji · Takeshi Arima · Hiroyuki Matsumoto · Masashi Kondo · Manabu Tokeshi · Yoshinori Hasegawa · Yoshinobu Baba

- Microchip size: 100 x 40 µm
- Small volume (drops of blood)
- Rapid (65 sec)
- Lecture by optical microscope, polarizer and argon lazer
- Good correlation with CEDIA or PETINIA

Interest for increased throughput

- Important for out-patient clinics to allow direct dose adjustment during the patient visit
  - Avoiding late call, misunderstanding or even new appointment
- For the emergency room to allow more rapidly discharge or hospitalisation
- To allow more time for PK calculations
- To increase laboratory efficiency

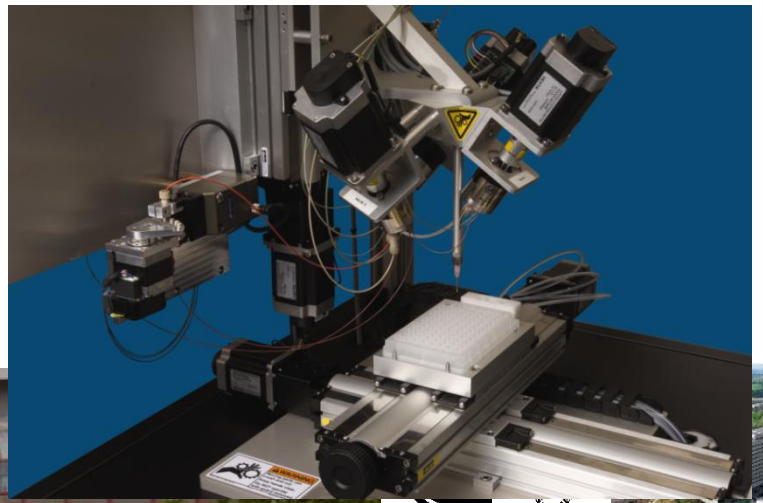
RapidFire SPE/MSMS

Ultra-fast autosampler & online SPE system

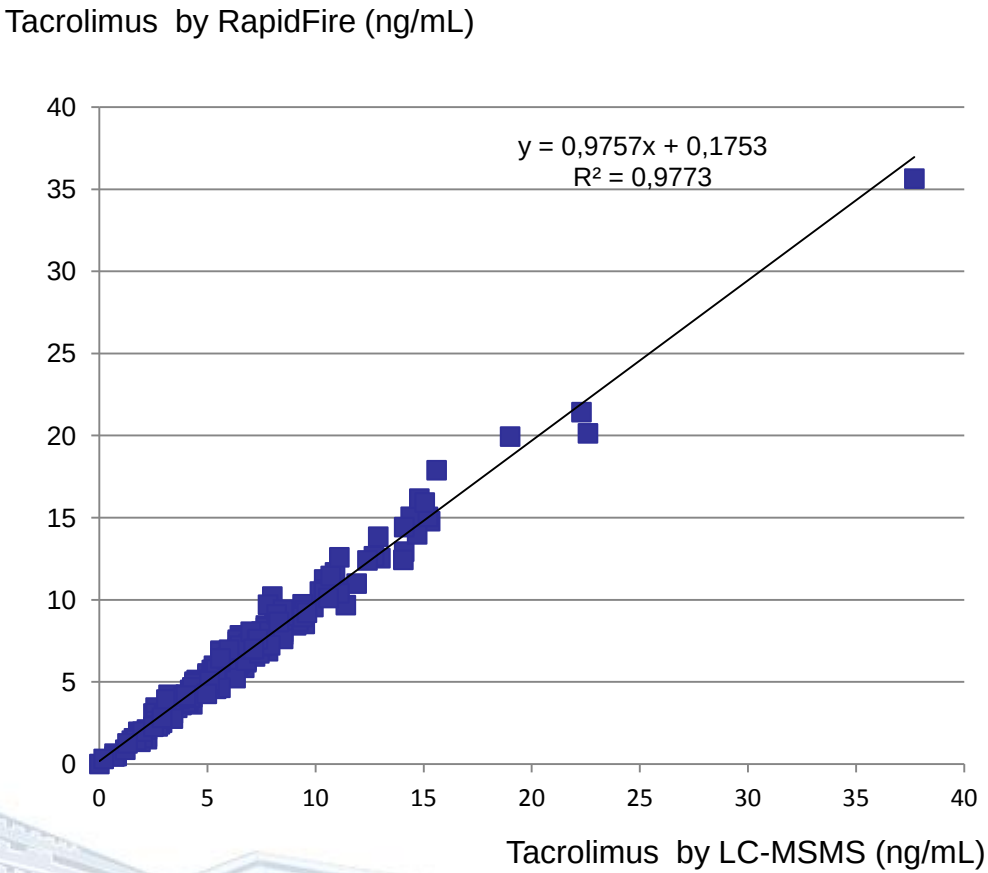
- Replaces LC in LC/MS
- Reusable SPE cartridge
- Integrates with standard ESI MS instruments
- **Cycle time = 7-13 s/sample**

Compatible with biological matrices

- Serum
- Plasma
- Whole blood
- Urine



Tacrolimus correlation (n: 220)



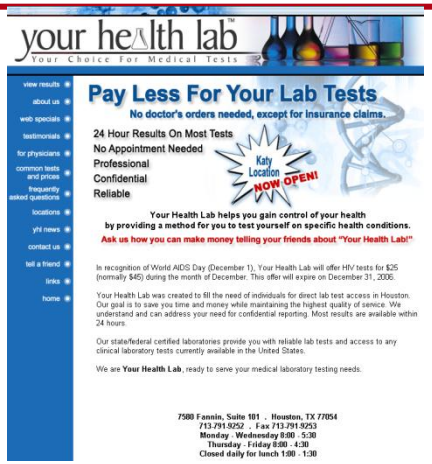
Third perspective of progress
Improve patient's quality of life

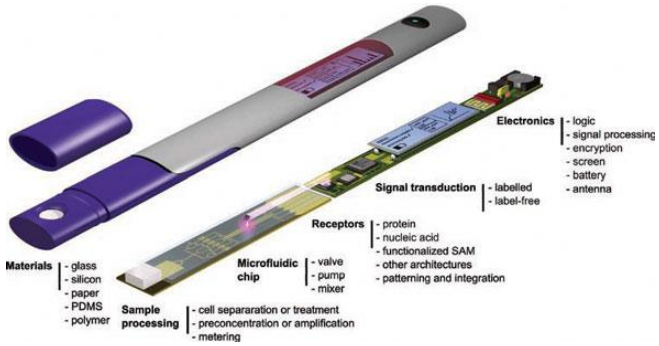
Improve patient's quality of life

- Reducing duration of hospitalisation and frequency of visits
- Hospitalisation
  - Initiation of therapy and optimisation of a personalized dosing regimen: *In-situ* nanotechnologies
  - Reduction of blood sampling
  - Reduction of drug interactions or dose adjustments
- Out-patient follow up
  - POCT
  - Dried spot
  - Home Telehealth

Possible evolutions:
the best or the worst

- DTC (Direct To Consumer testing)
  - Certified labs, but…
  - No need for doctor's order
  - Without any medical supervision and interpretation
- POCT testing
  - Increasing number of tests
  - Quality control
  - Interpretation





Possible evolutions:
the best or the worst

- Transdermal sensors
  - e.g. transdermal alcohol sensors bracelet device recording in real time alcohol consumption (wireless radiofrequency signal transmission to a modem)
    TR Leffingwell et al. Alcohol Clin Exp Res. 2013; 37:16-22

- Reverse iontophoresis could be used to extract some drugs from the skin
  - e.g. phenytoin, amikacin, lithium…
    F Marra et al. Int J Pharm. 2013; 440:216-20

- Need for improved standardization among analytical methods

Possible evolutions:
the best or the worst

- « Online » or « real-time » ultra-fast measurements
  - Emergence of nanotechnologies, nano-sensors…
  - Useful for immediate decision-making at bed-side

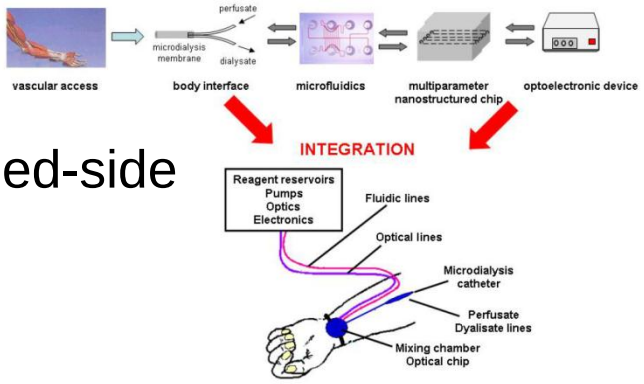
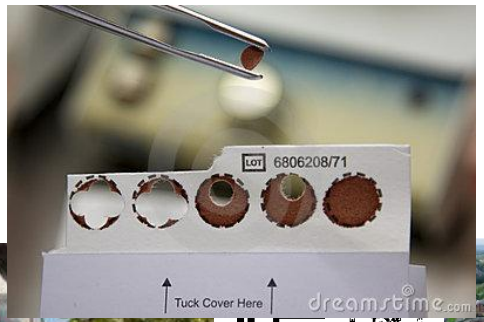


Figure 1. Diagram of the proposed POCT device.

- Home Telehealth (e-health, telemedicine)
  - Anticoagulation
  - Diabetes
  - Cardiac monitoring

- Home blood sampling
  - Dried Blood Spot



B Keevil, Clin Biochem 2011,44,110-18

Dried Blood Spot

- Still limited use in TDM but broad perspectives
- Advantages
  - Small volume of blood
    - Ethics: children, preclinical studies for industry on animals etc…
  - Flexibility and comfort for the patient (could be done at home)
  - No need to go to an out-patient clinic
  - Stability and shipment easier
- Challenges
  - Hct & blood viscosity effects *(Denniff et al Bioanalysis, 2010, 2, 1385-95)*
  - Analyte nature
  - Spotting technique
    - Quality of paper used
    - Temperature or humidity

Dried Blood Spot

- Applications
  - Anti-HIV drugs
  - Drugs of abuse
  - Benzodiazepines
  - Immunosuppressants
  - SSRI
  - Antiepileptics, etc…

B Keevil, Clin Biochem 2011,44,110-18

Dried Blood Spot

J. Am. Soc. Mass Spectrom. (2011) 22:1501–1507
DOI: 10.1007/s13361-011-0177-x

RESEARCH ARTICLE

Quantitative Analysis of Therapeutic Drugs in Dried Blood Spot Samples by Paper Spray Mass Spectrometry: An Avenue to Therapeutic Drug Monitoring

Nicholas Edward Manicke,[1] Paul Abu-Rabie,[2,3] Neil Spooner,[2] Zheng Ouyang,[4,5] R. Graham Cooks[1,5]

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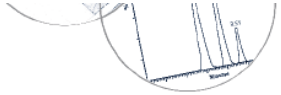
[4]Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN 47907, USA
[5]Center for Analytical Instrumentation Development, Purdue University, West Lafayette, IN, USA

- Generation of gas phase ions directly from blood card
- Reduced sample preparation: 30 sec
- LOD around 1 ng/mL

Dried Blood Spot



EBF recommendation on the validation of bioanalytical methods for dried blood spots

Over the last few years bioanalysts, pharmacokineticists and clinical investigators have rediscovered the technique of dried blood spots. The revival has provided pharmaceutical R&D a wealth of opportunities to optimize the drug-discovery and development process with respect to animal and patient ethics, new scientific insights and costs savings. On the bioanalytical front, multiple experiments have been performed and a lot of experience has been gained. Nevertheless, the technique still has a number of bioanalytical challenges. The European Bioanalysis Forum discussed the advantages and hurdles of the technique and summarized their current thinking in a recommendation on the validation of bioanalytical methods for dried blood spots, which can be used as a cornerstone for further discussions and experiments.

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Philip Timmerman[1†], Steve White[2], Susanne Globig[3], Silke Lüdtke[4], Leonarda Brunet[5] & John Smeraglia[6]

Take home message (1)

- TDM still has to face various challenges limiting its widespread use: different perspectives of progress
- Reinforcement of the PK-PD relationship
  - PopPK
  - Phamacodynamic biomarkers
  - Pharmacogenetics
  - Intracellular drug concentration
  - Standardization of the TDM approaches

Take home message (2)

- Analytical methods development
  - Standardization of the calibrators and methods
  - Automatisation/robustness
  - Emergence of nanotechnologies (Lab-on-Chip), online measurement
  - Increased throughput or TAT (few seconds per test)
- Patient's quality of life
  - Reduction of hospital stay and frequency of visits and blood drawing
  - Promotion of Dried Blood Spot testing
  - e-Health

Thank you for your attention