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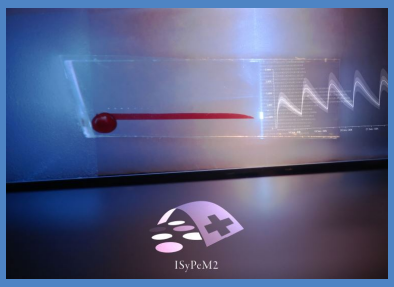
# ISyPeM II

## THERAPEUTIC DRUG MONITORING FOR PERSONALIZED MEDICINE

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**What it's about…**

***Developing a technological platform to improve medical practice by enabling personalized medicine via therapeutic drug monitoring, while reducing healthcare costs.***

**Context and project goals**

Modern therapeutics must benefit from the development and large-scale implementation of convenient, user-friendly, miniaturized, integrated instruments enabling drug concentration monitoring and seamless pharmacokinetically guided dosage individualization. Technological advances during recent years make it possible to envisage a portable system, which would allow to perform drug concentration measurement in patients receiving critical treatments. The device should be offered at affordable cost to specialized clinics, and progressively to general practices or even to the patients themselves (as it is already the case for blood glucose determination). Translation of concentration measurement values into personalized treatment advices requires the integration of efficient and ergonomic computer tools into the system. These need to be coupled with communication capabilities, which are nowadays becoming a standard in many aspects of medical care, in order to be connected to reference pharmacokinetic-parameters databases.

The conception of our Point-Of-Care (POC) system is addressed to respond to three main objectives:

- perform the measurement of drug concentration in blood samples by an automated and compact analytical setup
- provide the medical doctor with information on the behavior of the patient within the population and accordingly suggest dosage adjustment
- collect drug usage and measurement data into a remote database, enabling further refinements in dosage adjustment procedures.

The aim of this project is to develop a sample-to-result POC system, which would include all the outlined functions. In particular, the system will be stand-alone and provide communication and elaboration functions in a configurable fashion in order to respond to different application needs.

The ISyPeM consortium holds a composite set of know-how and owned technologies to develop each technological component of the system, namely: a miniaturized blood sample preparation device, connected to a compact and low-cost analytical system with electronic readout for determining the drug concentration; an embedded elaboration software framework to determine dosage adjustment, manage population data and connect with remote databases; finally, a flexible and ergonomic graphical user interface to interact with the user at different levels of complexity.

## How it differentiates from similar projects in the field

A comprehensive integrated approach to Therapeutic Drug Monitoring which combines innovative point-of-care compatible assays, prescription decision support and interoperability in a complex data-sharing scenario.

At present, no research work or commercial device addresses the measurement of small drug targets in a point-of-care format facing the challenge of the most hydrophobic and low-concentration drugs (such as tacrolimus) finding innovative solutions from the molecular probes to the detection system.

## Quick summary of the project status and key results

The novel aptamer-selection protocol developed by CLSE in the framework of the ISyPeM I project led to the selection of highly specific probe molecules for Tobramycin, which demonstrated their functionality in serum samples. On the other hand, specific monoclonal antibodies for tacolimus have been successfully selected.

Measurement system miniaturization let to drug detection on sample volumes down to 20 µl both for label-based and label-free techniques (whole blood and serum samples respectively).

The software user-interface EzeCHiel for therapeutic drug monitoring, which features the possibility to visualize the concentration curve, percentiles for population data, patient specific parameters and works on an encrypted local database, has been validated by CHUV for several drugs and it is currently employed by pharmacologists at the hospital.

A specification web interface to connect EzeCHiel and database management systems used in CHUV have been developed according to the standard of clinical data exchange and approved by CHUV.

PRS signed: All partners signed a Product Requirements Specifications document prepared by the HES-SO Valais. This demonstrates the motivation of the consortium toward a commonly agreed target and in particular to ensure the functionality of the demonstrators.

## Success stories

In collaboration with DBS System Sàrl, the partnership has developed a blood filtration microsystem. The quantity of plasma filtered from whole blood outperforms any passive on-chip method reported to date in the literature.

EzeCHiel: start-up being launched soon: Partners at HEIG-VD and at CHUV will create a start up based on the EzeCHiel software.

The first demonstrator for drug monitoring at the point-of-care developed by CLSE-EPFL and STMicroelectronics and based on an STMicroelectronics property CMOS image sensor, is capable of determining Tobramycin concentrations in serum samples.

### Presence in the media

“Le bon dosage en quelques minutes.”, E. Morisod, HES-SO Valais-Wallis Rapport d’activités 2013 (2013).

“Life Sciences HES-SO Valais//Wallis: Applied Research for Innovators”, E. Heinzelmann, Biotechnet Column in Chimia 68 (2014) 449.

“Imaginez un monde : bio-électronique”, Le Court du Jour, RTS1, 26.01.2015.

## Patent

WO 2014/020479 A2 , April 10, 2014. “Post-CMOS Processing and 3D Integration Based on Dry-Film Lithography", C. Guiducci, Y.Leblebici, Y. Temiz.

## Main publications


Verena Gotta, Stephane Bouchet, Nicolas Widmer, Peter Schuld, Laurent A. Decosterd, Thierry Buclin, Francois-Xavier Mahon, Chantal Csajka, Large-scale imatinib dose–concentration–effect study in CML patients under routine care conditions , Leukemia Research 38 (2014) 764–772, 2014 Elsevier Ltd.

F. M. Spiga, A. Bonyár, B. Ring, M. Onofri, A. Vinelli, H. Sántha, C. Guiducci, G. Zuccheri, Hybridization chain reaction performed on a metal surface as a means of signal amplification in SPR and electrochemical biosensors, Biosensors and Bioelectronics, 54, (2014), pp. 102-108.

E. Accastelli, G. Cappi, J. Buckley, T. Ernst, C. Guiducci, Comparison between front- and back-gating on silicon nanoribbons in real-time sensing experiments, Nanotechnology (IEEE-NANO), 2013 13th IEEE Conference, pp.517,520, 5-8 Aug. 2013.

A Fuchs, PharmD, M Guidi, PhD, E Giannoni, MD, D Werner, PharmD, PhD, T Buclin, MD, N Widmer, PharmD, PhD, C Csajka, PharmD, PhD, Population pharmacokinetic study of gentamicin in a large cohort of premature and term neonates, British Journal of Clinical Pharmacology, DOI: 10.1111/bcp.12444.

V. Balasubramanian, P.-F. Ruedi, Y. Temiz, A. Ferretti, C. Guiducci, and C. C. Enz, A 0.18 Biosensor Front-End Based on Noise, Distortion Cancelation and Chopper Stabilization Techniques, IEEE Trans. Biomed. Circuits Syst., vol. 7, no. 5, pp. 660–673, Oct. 2013.

G. Cappi, E. Accastelli, F. M. Spiga, V. Cantale, M. A. Rampi, L. Benini, and C. Guiducci, A portable setup for molecular detection by transmission LSPR, Materials Research Society Symposium Proceedings, 2013, vol. 1479, pp. 27–32.

G. Cappi, E. Accastelli, V. Cantale, M. A. Rampi, L. Benini, and C. Guiducci, Peak shift measurement of localized surface plasmon resonance by a portable electronic system, Sens. Actuators B Chem., vol. 176, pp. 225–231, 2013.

E. Petit-Jean, T. Buclin, M. Guidi, E. Quoix, B. Gourieux, L.A. Decosterd, A. Gairard-Dory, G. Ubeaud-Séquier, N. Widmer, Erlotinib: Another Candidate for the Therapeutic Drug Monitoring of Targeted Therapy of Cancer? A Pharmacokinetic and Pharmacodynamic Systematic Review of Literature, Ther Drug Monit. Feb, 2015; 37(1) pp. 2-21.

E. Accastelli, F. M. Spiga, T. Ernst, and C. Guiducci, Detection of PCR amplification by top-down silicon nanowires field effect transistors, Proceedings of the EMBS Micro and Nanoengineering in Medicine Conference, Oahu, Hawaii USA, 2014.

G. Cappi, F. M. Spiga, Y. Moncada, A. Ferretti, M. Beyler, M. Bianchessi, L. Decosterd, T. Buclin, and C. Guiducci, Label free detection of Tobramycin in Serum by Transmission Localized Surface Plasmon Resonance, ACS Analytical Chemistry.

F. M. Spiga, P. Maietta, and C. Guiducci, More DNA aptamers for small drugs: a capture−SELEX coupled with Surface Plasmon Resonance and High-Throughput Sequencing, ACS Combinatorial. Science., 2015.

A. Dubovitskaya, V. Urovi, M. Vasirani, K. Aberer, M. Schumacher, A Cloud-based eHealth Architecture for Privacy Preserving Data Integration, in: Proceedings of the 30th IFIP TC-11 SEC 2015 International Information Security and Privacy Conference, IFIP, Springer Science and Business Media, 2015 .

Simalatsar, A.; Bornet, R.; Wenqi You; Thoma, Y.; De Micheli, G., Safe Implementation of Embedded Software for a Portable Device Supporting Drug Administratio, 2014 IEEE International Conference on Bioinformatics and Bioengineering (BIBE), ,pp.257,264, 10-12 Nov. 2014.


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**“Personalized treatments enabled by distributed patient monitoring and data communication in complex data-sharing scenari”**