OncoProteomics Laboratory Progress Report 2016-2020

Core Facility Mass Spectrometry-based Proteomics of Amsterdam UMC

Introduction

To better understand cancer in all its facets and work towards improved diagnostics and treatment of cancer, the OncoProteomics Laboratory of the Amsterdam UMC focusses on the direct global analysis of the functional building blocks of life, *i.e.*, the proteins which activity and functions are highly deranged in cancer cells. Unbiased (phospho)protein profiling by mass spectrometry-based proteomics offers a means to measure the biochemical impact of cancer-related genomic abnormalities, and thereby can bridge the gap between cancer genome information and observed cancer phenotype (Figure 1). **Therefore, OncoProteomics is of high interest for all programs/ themes of the Cancer Center Amsterdam of the Amsterdam UMC.**

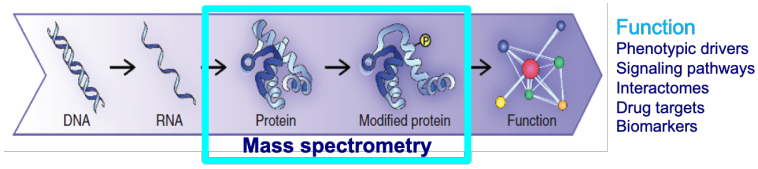
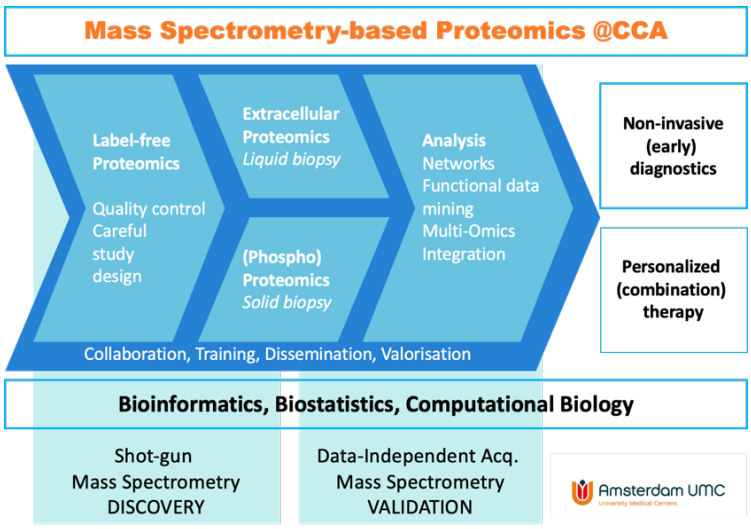


Figure 1. Proteomics, global analysis of the functionally relevant -OME

In collaboration with cancer researchers and clinicians of the CCA and external collaborators, our studies encompass the full spectrum of analyses in cancer cell lines, organoids, mouse models (both genetic and patient-derived xenografts) and clinical samples. The latter is enabled by our embedding in a clinical department *(*Medical Oncology) at Amsterdam UMC and our ample contacts with clinicians. **This setting ensures working on real clinical needs, which is key to the mission of the Cancer Center Amsterdam.**

The multi-disciplinary OPL team includes core members with expertise in mass spectrometry, biology, biochemistry, and bioinformatics, and post-docs and PhD students with life science and clinical background (for more information, see www.oncoproteomics.nl). Since its foundation in **2006** with a **start-up grant of the Cancer Center Amsterdam**, the OPL has acquired a strong reputation as cancer proteomics center. Robust label-free quantitation strategies and dedicated statistics have been developed for protein expression profiling and biomarker and drug target discovery (J. Prot. Res. 2010; J. Prot. 2014; Mol. Syst. Biol. 2019; Bioinformatics 2010, 2012, 2016, 2020).

Over the years, we have shared our know-how and provided high quality mass spectrometry data to CCA and Amsterdam UMC researchers and beyond. Our proven ability to collaborate can be evidenced from the multiple CCA and KWF projects with Jimenez as (co)PI or collaborator and investigators at CCA and multiple national institutes (see below for an overview of the on-going cancer proteomics research collaborations).



We strongly believe that multi-disciplinary collaboration is key to achieve higher impact science with the ultimate goal to have clinical impact.

Cancer proteomics research @OPL

Our OncoProteomics research can be divided into two broad cancer research lines (figure 2):
1. Analysis of tumor microenvironment, via secretome, exosome and proximal fluid proteomics to develop **non-invasive biomarker applications**
2. Analysis of cancer signalling pathways via intracellular (phospho)proteomics to enable **target discovery, patient stratification and response prediction.**

These research lines have been successfully applied in many **collaborative projects** in various tumor types, including colorectal cancer, breast cancer, lung cancer, pancreatic cancer, prostate cancer and leukemias (see overview in appendix). The obtained (phospho)proteome data provide a valuable addition to the existing large collections of DNA and RNA datasets, thereby contributing to the multi-omics perspective of cancer and its precursors and have revealed novel candidate biomarkers and drug targets that are in different phases of validation.
A highlight of research line 1 is the discovery and validation of novel stool markers for colorectal cancer screening using stool proteomics (Ann. Intern. Med. 2017). Antibody assays for the top 10 protein stool markers are currently being tested in prospective validation cohorts with so far positive results. Another highlight is the urine exosome proteomics work that reveals the potential for not only non-invasive prostate cancer detection but also for non-invasive pan-cancer detection. Non-cancer highlights include our CSF proteomics efforts to discover and validate biomarkers for Alzheimer's Disease and other dementias.
A highlight of research line 2 is the successful downscaling of the phosphotyrosine workflow (J.Prot. 2017) and recent application in a clinical trial setting (Cancers 2020), underscoring the feasibility of clinical phosphoproteomics. In the coming years, we aim to perform phosphoproteomics on tumor biopsies collected in multiple clinical trials to develop improved patient selection for targeted therapy. Our newly developed computer algorithms that can pinpoint highly active protein kinases in single biological samples on the basis of label-free phosphoproteomic data (Integrative Inferred Kinase Activity (INKA) analysis, Mol. Syst. Biol. 2019) will be a key component of a future multi-omics personalized medicine pipeline. Its value was recently shown in the preclinical setting in several published studies.
We anticipate that a combined multi-OMICs view of the tumor of a patient, that includes not only the genome but also the functionally relevant proteome and phosphoproteome, will be essential to revolutionize molecular cancer therapy and deliver on the promise of personalized medicine.

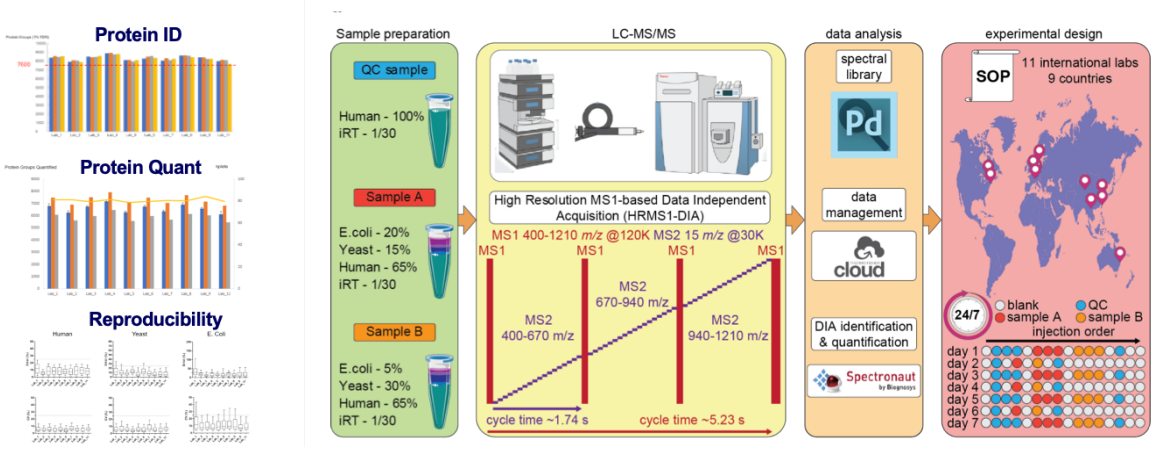


Fig. 3. Robust, sensitive, and reproducible data generation across eleven sites in nine countries on seven consecutive days in a 24/7 operation mode.

New developments in clinical cancer proteomics

One exciting new development is next generation quantitative proteomics based on data-independent acquisition (DIA) mass spectrometry. This novel approach was the focus of the NWO-Middelgroot grant that Jimenez acquired in 2016. DIA-MS uses parallel peptide fragmentation and

less complex biochemical workflows, together reducing missing values, processing time and costs, thereby enabling large scale clinical proteomics. DIA-MS will be key for phosphoproteomics for precision oncology. After implementing and bench-marking DIA-MS at the OPL, we participated in a multi-center study, conducted in nine countries. We showed that harmonized MS with standardized data acquisition can yield highly reproducible data (Fig. 3. Xuan et al., Nature Communications, 2020).

Moreover, last year Jimenez initiated a **multi-laboratory collaborative cancer proteome profiling effort**, a la TCGA, that represents **T**he mass spectrometry-based **C**ancer **P**roteome **A**tlas (**TCPA**) project (pilot atlas with 325 cancer samples shown in Figure). Many CCA PIs supplied tumor tissue for this exciting effort. **The global aims of the analysis will be: 1. to better understand the molecular underpinnings of cancer; 2. to identify core and cancer type enriched molecular therapeutic targets and biomarkers.**

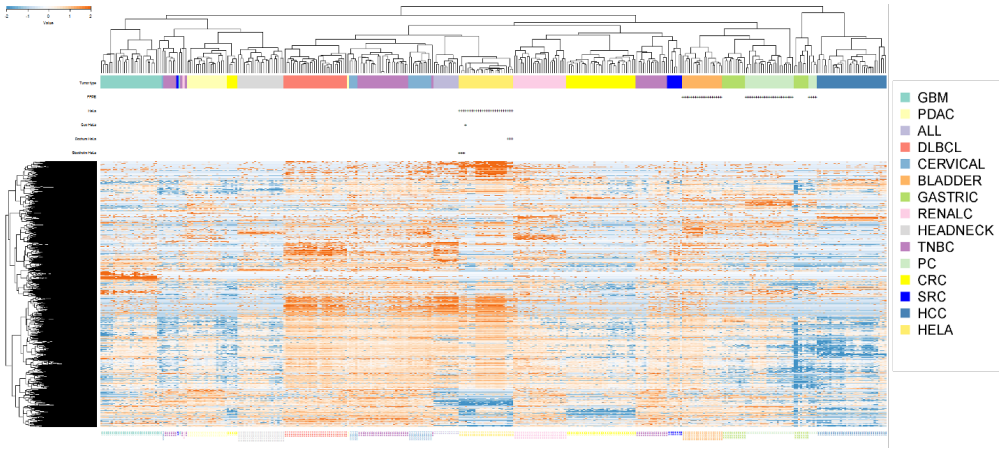


Figure 4. DIA-MS to generate pan-cancer atlas. Unsupervised cluster analysis using the first set of 325 Amsterdam tumor proteomes and Hela reference proteomes from all participating laboratories. Please note that all Hela samples cluster together, underscoring the feasibility of TCPA based on highthroughput DIA-MS.

Currently 6 clinical proteomics laboratories across Europe and Asia participate and have submitted data for integration into the atlas. A first collaborative manuscript reporting a deep mass spectral library based on deep cancer proteomes for > 15 tumor types has been submitted this year. We recently completed data generation for a draft 1.0 atlas, consisting of 1000 cancer proteomes for ~20 tumor types. This unique dataset will be subjected to advanced data mining and the results will be reported in 2021.

Proteomics support to users

As proteomics core facility, OPL provides support in all the steps of a proteomics experiment: study design (discussed at project intake with head OPL) and sample preparation step (research technician Dr. Richard de Haas), mass spectrometry (Dr. Sander Piersma) and dedicated analysis (Dr. Thang Pham). The analysis result is submitted in a user-friendly excel file to the end-users by Dr. Pham. Miscellaneous logistics support and optional support in functional data mining is given by Dr. Jaco Knol. For more information, see our website www.oncoproteomics.nl.

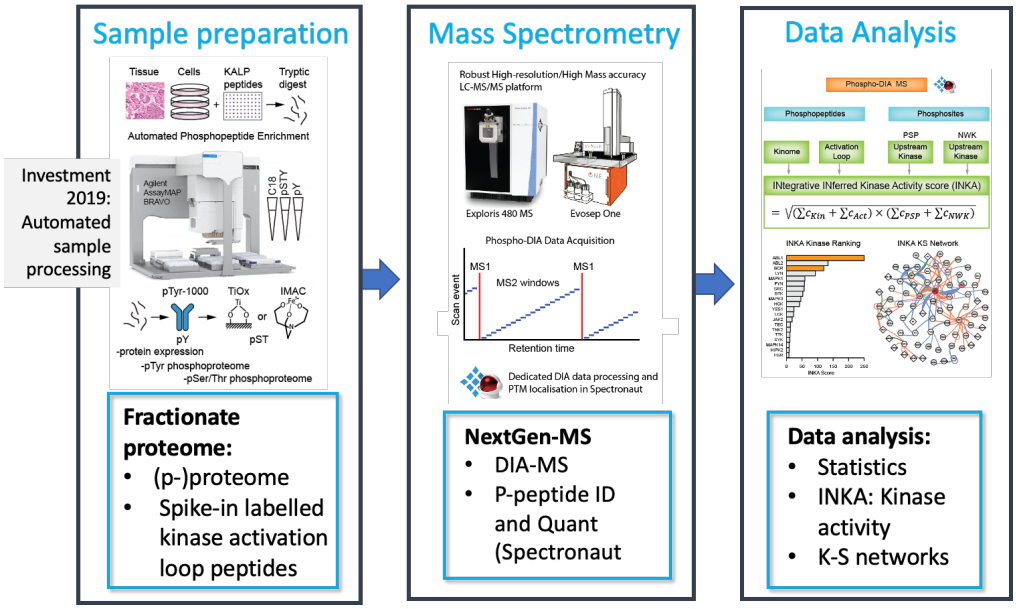


Figure 5. Steps proteomics experiment. To enable "full service" support to users, we acquired the Bravo station and recently automated the global phosphoproteomics workflow.

To showcase what we achieved in the past 5 years, the next sections of this report provide:

- An overview of the major collaborative research and publications 2015-2020 (**pages 4-14**)
- A listing of publications related to OncoProteomics methodology development (pages **15-16**)
- Publications based on smaller collaborations/ core facility functions (**pages 17-18**)
- Listing of users with experiments in progress (**page 18**)
- Collaborator quotes (**pages 19-23**)
- An appendix with OncoProteomics Facts and Figures (**pages 24**)
- An appendix with abstracts of on-going and completed projects employing proteomics in the past 5 years **pages 25-xx**)

OncoProteomics Collaborative Projects past 5 years

Denote projects that yielded funding for OPL core group members who are crucial for the facility

*Phosphoproteomics for precision medicine (on-going)

Name Collaborators: **Dr. Mariette Labots, Dept. Medical Oncology, Prof.dr. Henk Verheul (RadboudUMC), et al. Medical Oncology.**

Mass spectrometry-based phosphoproteomics analyses of cancer cell lines and tumor needle biopsies collected in clinical trials

- This work was initiated with funding by Vitromics Health Care. In preparation for June 2020 round: KWF consortium grant "Dutch Multi-Omics Cancer Moonshot" that aims to profile needle biopsies collected by the national Center for Personalized Cancer Treatment and develop a multi-omics precision oncology analysis pipeline.
- Expected in 2021: Analysis of needle biopsies collected in the Reposit phase II study (Drs. Van der Hiel (NKI) and Dr. A.J.M. van den Eertwegh (Medical Oncology)) "**Re**sponse Monitoring and Resistance Prediction with **Posi**tron Emission Tomography and **T**umor Characteristics" to identify predictive markers.

Manuscripts in preparation:

- H. van der Wijngaart, R. Beekhof, JC. Knol, A. Henneman, R. de Goeij, S. Piersma, TV. Pham, C.R. Jimenez, HMW. Verheul, M. Labots. **Predictive biomarkers for response to sunitinib in patients with Renal Cell Carcinoma**.
- ME van Linde, M Labots, CG Brahm, KE Hovinga, PC de Witt Hamer, RJ Honeywell, R de Goei-Haas, H Dekker, SR Piersma, T Pham, WP Vandertop, CR Jiménez, HMW Verheul. **Tumor drug concentration and phosphoproteomic profiles after two weeks of treatment with sunitinib in patients with newly diagnosed glioblastoma.**
- Tineke E. Buffart, Rosanne A.H.M. van den Oord, Adriënne van den Berg, Riet Hilhorst, Niek Bastiaensen, Hans F.M. Pruijt, Adriaan van den Brule, Peet Nooijen, Mariette Labots, Richard R de Goeij-de Haas, Henk Dekker, Sander R. Piersma, Thang V. Pham, Theo van der Leij, Rik de Wijn, Rob Ruijtenbeek, Connie R., Jiménez, Henk M.W. Verheul. **Time dependent effect of cold ischemia on the phosphoproteome and protein kinase activity in colorectal cancer tissue freshly obtained from patients.**
- Tineke E. Buffart et al. **Phosphoproteomics of right and left-sided colon cancers reveals differentially activated drug targets.**

Publications:

- Labots M, Pham TV, Honeywell RJ, Knol JC, Beekhof R, de Goeij-de Haas R, Dekker H, Neerincx M, Piersma SR, van der Mijn JC, van der Peet DL, Meijerink MR, Peters GJ, van Grieken NCT, Jiménez CR, Verheul HMW. **Kinase Inhibitor Treatment of Patients with Advanced Cancer Results in High Tumor Drug Concentrations and in Specific Alterations of the tumor phosphoproteome.** Cancers 2020 Feb 1;12(2) pii: E330.
- van der Hiel B, Haanen JBAG, Stokkel MPM, Peeper DS, Jimenez CR, Beijnen JH, van de Wiel BA, Boellaard R, van den Eertwegh AJM; REPOSIT study group. **Vemurafenib plus cobimetinib in unresectable stage IIIc or stage IV melanoma: response monitoring and resistance prediction with positron emission tomography and tumor characteristics (REPOSIT): study protocol of a phase II, open-label, multicenter study.** BMC Cancer. 2017 Sep 15;17(1):649.
- van der Mijn JC, Broxterman HJ, Knol JC, Piersma SR, De Haas RR, Dekker H, Pham TV, Van Beusechem VW, Halmos B, Mier JW, Jiménez CR, Verheul HM. **Sunitinib activates Axl signaling in renal cell cancer.** Int J Cancer. 2016 Jun 15;138(12):3002-10.
- Methodology development: Labots M, van der Mijn JC, Beekhof R, Piersma SR, de Goeij-de Haas RR, Pham TV, Knol JC, Dekker H, van Grieken NCT, Verheul HMW, Jimenez CR.

Phosphotyrosine-based-phosphoproteomics scaled-down to biopsy level for analysis of individual tumor biology and treatment selection. J Proteomics. 2017 Apr 23. pii: S1874-3919(17)30140-9.

- van der Mijn JC, Labots M, Piersma SR, Pham TV, Knol JC, Broxterman HJ, Verheul HM, Jiménez CR. **Evaluation of different phospho-tyrosine antibodies for label-free phosphoproteomics**. J Proteomics. 2015 Sep 8;127(Pt B):259-63.

* Interrogating the (phospho)proteome for drug targets in pancreatic cancer (on-going)

Name Collaborators: ***Prof.dr. Geert Kazemier (Surgery), Dr. Elisa Giovannetti (Medical Oncology), Dr. Maarten Bijlsma (Lexor), Prof.dr. Hanneke van Laarhoven (Lexor/Medical Oncology)***

Phosphoproteomics analyses of patient-derived xenograft models developed by my collaborators and of clinical samples and functional testing of potential drug targets.

- Shared PhD student in the context of a VUmc-AMC alliance project. The data of the alliantie project were used to obtain funding from KWF to continue and expand the project with currently 2 PhD students working on the project.
- KWF VU2016-1012 project (PI Jimenez, coPIs Bijlsma and Giovannetti)

In preparation/ submitted manuscripts:

- Vallés-Martí A, Mantini G, Le Large T.S., Pham T.V., Piersma S.R., Knol J.C., Kazemier G, Laarhoven, H, Bijlsma M.F., Giovannetti E., Jiménez C.R. **Individualized low-drug combinations in PDAC: a phosphoproteomic approach.**
- T.Y.S. Le Large et al. **Focal adhesion kinase inhibition synergizes with nab-paclitaxel to target pancreatic ductal adenocarcinoma.**

Publications:

- Mantini G, Vallés AM, Le Large TYS, Capula M, Funel N, Pham TV, Piersma SR, Kazemier G, Bijlsma MF, Giovannetti E, Jimenez CR. **Co-expression analysis of pancreatic cancer proteome reveals biology and prognostic biomarkers.** Cell Oncol (Dordr). 2020 Dec;43(6):1147-1159.
- Le Large TY, Mantini G, Meijer LL, Pham TV, Funel N, van Grieken NC, Kok B, Knol J, van Laarhoven HW, Piersma SR, Jimenez CR, Kazemier G, Giovannetti E, Bijlsma MF. **Microdissected pancreatic cancer proteomes reveal tumor heterogeneity and therapeutic targets.** JCI Insight. 2020 Aug 6;5(15):e138290.
- Le Large TYS, Meijer LL, Paleckyte R, Boyd LNC, Kok B, Wurdinger T, Schelfhorst T, Piersma SR, Pham TV, van Grieken NCT, Zonderhuis BM, Daams F, van Laarhoven HWM, Bijlsma MF, Jimenez CR, Giovannetti E, Kazemier G. **Combined Expression of Plasma Thrombospondin-2 and CA19-9 for Diagnosis of Pancreatic Cancer and Distal Cholangiocarcinoma: A Proteome Approach.** Oncologist. 2020 Jan 14.
- Le Large TYS, El Hassouni B, Funel N, Kok B, Piersma SR, Pham TV, Olive KP, Kazemier G, van Laarhoven HWM, Jimenez CR, Bijlsma MF, Giovannetti E. **Proteomic analysis of gemcitabine-resistant pancreatic cancer cells reveals that microtubule-associated protein 2 upregulation associates with taxane treatment.** Ther Adv Med Oncol. 2019 Ma 10;11:1758835919841233.
- Le Large TYS, El Hassouni B, Kazemier G, Piersma SR, van Laarhoven HWM, Bijlsma MF, Jimenez CR, Giovannetti E. **Multidrug-resistant transporter expression does not always result in drug resistance.** Cancer Sci. 2018 Oct;109(10):3360-3362.
- Le Large TY, Bijlsma MF, Kazemier G, van Laarhoven HM, Giovannetti E, Jimenez CR. **Key biological processes driving metastatic spread of pancreatic cancer as identified by multi-omics studies.** Semin. Cancer Biol. 2017 Mar30.

- Le Large TYS, Meijer LL, Paleckyte R, et al. **Combined Expression of Plasma Thrombospondin-2 and CA19-9 for Diagnosis of Pancreatic Cancer and Distal Cholangiocarcinoma: A Proteome Approach.** Oncologist. 2020;25(4):e634,Äêe643.
- Mantini G, Meijer LL, Glogovitis I, In 't Veld SGJG, Paleckyte R, Capula M, Le Large TYS, Morelli L, Pham TV, Piersma SR, Frampton AE, Jimenez CR, Kazemier G, Koppers-Lalic D, Wurdinger T, Giovannetti E. Omics **Analysis of Educated Platelets in Cancer and Benign Disease of the Pancreas**. Cancers (Basel). 2020 Dec 29;13(1):66.

*Phosphoproteomics analysis to enable precision medicine for anti-EGFR therapy in colorectal cancer (on-going)

Name Collaborators: **Prof.dr. Livio Trusolino (Italy) and Prof.dr. Henk Verheul (Medical Oncology)**

Large-scale mass spectrometry-based proteomics and phosphoproteomics analyses of a unique collection of patient-derived xenograft models of colorectal cancer (n=150) that were developed and genomically characterized by Trusolino.

- Orals by PhD student Robin Beekhof at AACR2016 and HUPO2017.
- Based on preliminary data on 29 PDX models, a new KWF consortium grant was acquired (1.1 MEuro) with start in 2020 that includes also Prof.dr. Lodewyk Wessels (NKI) as coPI.

Manuscript in preparation:

- Robin Beekhof, Andrea Bertotti, Valentina Vurchio, Francesca Cottino, Eugenia R. Zanella, Giorgia Migliardi, Alex A. Henneman, Jaco C. Knol, Richard R. de Haas, Sander R. Piersma, Mariette Labots, Henk M.W. Verheul, Livio Trusolino, Connie R. Jimenez. **The phosphoproteomic landscape associated with sensitivity and resistance to EGFR blockade in colorectal cancer.**

Publication:

- Beekhof R, van Alphen C, Henneman AA, Knol JC, Pham TV, Rolfs F, Labots M, Henneberry E, Le Large TY, de Haas RR, Piersma SR, Vurchio V, Bertotti A, Trusolino L, Verheul HM, Jimenez CR. **INKA, an integrative data analysis pipeline for phosphoproteomic inference of active kinases.** *Mol Syst Biol*. 2019 Apr 12;15(4):e8250.

* Discovery and clinical validation of novel protein biomarkers for homologous recombination deficient breast cancer (on-going)

Name Collaborators: **Prof.dr. Jos Jonkers (NKI); Prof.dr. Sven Rottenberg (NKI); Prof.dr. Paul van Diest (UMCU)**

Mass spectrometry-based analyses of genetic mouse models of breast cancer and currently of a large collection of patient-derived xenograft models of breast cancer by proteomics and phosphoproteomics

- The collaboration was first supported by a **CCA** grant and later supported by **KWF project: VU2013-6020** (PI Jimenez, coPIs Jonkers, Van Diest) that was extended.

Manuscript in preparation:

- F. Rolfs, S. Piersma, T. Pham, J. Knol, P. ter Brugge, R. de Bruijn, J. Wesseling, E. Marangoni, V. Serra, J. Jonkers* & C. R. Jimenez*. **Identification and validation of protein biomarkers for homologous recombination deficiency in breast cancer using patient-derived xenograft models**

Publications:

- Warmoes M, Lam SW, der Groep PV, Jaspers JE, Smolders YH, de Boer L, Pham TV, Piersma SR, Rottenberg S, Boven E, Jonkers J, van Diest PJ, **Jimenez CR**. **Secretome proteomics reveals**

candidate non-invasive biomarkers of BRCA1 deficiency in breast cancer. Oncotarget. 2016 Sep 27;7(39):63537-63548.

- Warmoes M, Jaspers JE, Xu G, Sampadi BK, Pham TV, Knol JC, Piersma SR, Boven E, Jonkers J, Rottenberg S*, **Jimenez CR***. **Proteomics of genetically engineered mouse mammary tumors identifies fatty acid metabolism members as potential predictive markers for cisplatin resistance.** Mol Cell Proteomics. 2013 May;12(5): 1319-34. **Shared senior authorship*.
- Warmoes MO, Jaspers JE, Pham TV, Piersma SR, Massink MPG, Waisfisz Q, Rottenberg S, Boven E, Jonkers J, **Jimenez CR**. **Proteomics of mouse BRCA1-deficient mammary tumors identifies DNA repair proteins with diagnostic and prognostic value in human breast cancer.** Mol Cell Proteomics. 2012 Jul;11(7): M111.013334.
- Rolfs, F; Gogola, E; Piersma, S; Pham, T; Knol, J; Rottenberg, S; Jonkers, J; Jimenez, C. (2018). PO-019 **Phosphoproteomics to characterise dna damage response in mouse mammary tumours of different parp inhibitor susceptibility**. ESMO Open. 3. A28.3-A28. 10.1136/esmoopen-2018-EACR25.67.

* Response prediction for cisplatin-based treatment regimens in non-small cell lung cancer using a protein-based assay (on-going)

Name Collaborators: **Dr. Idris Bahce (Dept. Pulmonology), Dr. Teodora Radonic (Dept. Pathology) Prof.dr. Anton Berns (NKI), Dr. Sjoerd Burgers (NKI), Prof.dr. Egbert Smit (NKI)**

Mass spectrometry-based proteomics analyses of patient material selected based on clinical need and criteria defined by the clinical collaborators by post-doc of the OPL

- The collaboration is supported by an **ongoing KWF project VU2014-6816** (title as above; PI Jimenez, coPIs Burgers and Grunberg)

Manuscript in preparation:

- Franziska Böttger, Idris Bahce, Teodora Radonic, Sander R. Piersma, Erik Thunnissen, Sjaak A. Burgers, Egbert F. Smit, Kim Monkhorst, Connie R. Jimenez. **Identification of protein biomarkers for prediction of response to platinum-based treatment regimens in non-small cell lung cancer.**

Publication:

- Franziska Böttger, Tieneke B.M. Schaaij-Visser, Inge de Reus, Sander R. Piersma, Thang V. Pham, Remco Nagel, Ruud H. Brakenhoff, Erik Thunnissen, Egbert F. Smit, Connie R. Jimenez. **Proteome Analysis of Non-Small Cell Lung Cancer Cell Line Secretomes and Patient Sputum Reveals Biofluid Biomarker Candidates for Cisplatin Response Prediction**. J Proteomics. 2019 Mar 30;196:106-119.

Side-project: Characterization of tumor heterogeneity and cisplatin sensitivity in mouse models of small cell lung cancer

Design and execution of mass spectrometry-based proteomics experiments on tumor material from mouse models and analysis and visual representation of the data by post-doc of the OPL

Publication:

- Franziska Böttger*, Ekaterina A. Semenova*, Ji-Ying Song, Jan van der Vliet, Miranda Cozijnsen, Giustina Ferone, Rajith Bhaskaran, Lorenzo Bombardelli, Sander R. Piersma, Thang V. Pham, Connie R. Jimenez*, Anton Berns*. **Tumor heterogeneity underlies differential cisplatin sensitivity in mouse models of small cell lung cancer**. Cell Rep. 2019 Jun 11;27(11):3345-3358.e4.

* Urinary extracellular vesicles and their content as novel markers for minimally invasive diagnosis and prognosis of prostate cancer (on-going)

Name Collaborators: **Dr. Irene Bijnsdorp (Dept. Urology) Prof.dr. Guido Jenster (ErasmusMC), Prof.dr. Jack Schalken (RadboudMC)**

Proteomics of urinary vesicles of patients with prostate cancer as part of a multi-OMICs effort to develop novel biomarkers

- **KWF/Alpe d'Huzes EMCR 2015-8022**, PI Jenster, coPIs Jimenez, Schalken

Manuscripts in preparation:

- Erozenci LA, Pham TV, Piersma SR, Dits NFJ, van Royen ME, Moorselaar RJA, Jimenez CR, Bijnsdorp IV. **Urine storage protocol that is feasible with extracellular vesicle research and LC-MS/MS proteomics**
- Erozenci LA, Piersma SR, Pham TV, Bijnsdorp IV, Jimenez CR **Longitudinal landscape of urinary EV proteome reveals stable protein expression patterns within and between individuals**
- Erozenci LA, Feenstra, F, Piersma SR, PhamTV, Wortel, J, Jenster, G, Bijnsdorp, IV, Jimenez, CR. **Identification of the pan-cancer extracellular vesicle surface proteome and its application to detect prostate cancer in urine.**
- Erozenci LA, Piersma SR, Pham TV, Van Moorselaar J, Vis A, Jenster G, Schalken J, Verhaegh G, Bijnsdorp IV, Jimenez CR. **The urinary extracellular vesicle proteome of prostate cancer reveals distinct expression patterns and promising biomarkers**

Publications:

- Erozenci LA, Böttger F, Bijnsdorp IV, Jimenez CR. **Urinary exosomal proteins as (pan-)cancer biomarkers: insights from the proteome.** FEBS Lett. 2019 Jul;593(13):1580-1597.
- Bijnsdorp IV, Jimenez CR. **Large-Scale Urinary Proteome Dataset Across Tumor Types Reveals Candidate Biomarkers for Lung Cancer**. EBioMedicine. 2018 Apr;30:5-6.
- Bijnsdorp IV, Maxouri O, Kardar A, Schelfhorst T, Piersma SR, Pham TV, Vis A, van Moorselaar RJ, Jimenez CR. **Feasibility of urinary extracellular vesicle proteome profiling using a robust and simple, clinically applicable isolation method.** J Extracell Vesicles. 2017 Apr 28;6(1):1313091.
- Bijnsdorp IV, Schelfhorst T, Luinenburg M, Rolfs F, Piersma SR, de Haas RR, Pham TV, Jimenez CR. **Feasibility of phosphoproteomics to uncover oncogenic signalling in secreted extracellular vesicles using glioblastoma-EGFRVIII cells as a model**. J Proteomics. 2021 Feb 10;232:104076.

Phosphoproteomics for target discovery and response prediction in acute myeloid leukemia (on-going)

Name Collaborators: **Prof.dr. Jacqueline Cloos, Dr. Jeroen Janssen, Dept. Hematology**

Mass spectrometry-based phosphoproteomics analyses of cancer cell lines and patient samples from the biobank of my hematology collaborators

- Joint project funded by **CCA** with PhD student Caroline van Alphen. Work is now continued by second PhD student (David Cucchi) funded by the Dept. Hematology. Grant proposals have been submitted to Pharma to further clinical validate our results.
- Orals by PhD student Carolien van Alphen at several meetings including HUPO2017.

Manuscript in preparation:

- DGJ Cucchi, C van Alphen, S Zweegman, B. van Kuijk, Z. Kwidama, R De Haas, T Pham, S Piersma, JJWM Janssen, CR Jimenez, J Cloos. **Phosphoproteomic profiling of primary AML samples to predict *ex vivo* response to FLT3-inhibitors.**

- Carolien van Alphen, David Cucchi, Richard de Haas, Sander Piersma, Jacqueline Cloos, Jeroen Janssen, Connie Jimenez. **Ischemia-induced temporal phosphorylation patterns in primary acute myeloid leukemia samples** Accepted for publication by Mol. Cell. Prot.

Publications:

- Carolien van Alphen, Jacqueline Cloos, Sander R. Piersma, Jaco C. Knol, Thang V. Pham, Johan van Meerloo, Gert J. Ossenkoppele, Henk MW. Verheul, Jeroen JWM. Janssen* and Connie R. Jimenez* **Phosphotyrosine-based phosphoproteomics of a panel AML cell lines reveals oncogenic signaling and hyperactive tyrosine kinases as targets for treatment**. Mol. Cell.Prot. 2020, Feb. 26.

Other AML proteomics publications with Prof.dr. Cloos and Prof.dr. Zweegman:

- Wojtuszkiewicz A, Schuurhuis GJ, Kessler FL, Piersma SR, Knol JC, Pham TV, Jansen G, Musters RJ, van Meerloo J, Assaraf YG, Kaspers GJ, Zweegman S, Cloos J*, Jimenez CR*. **Exosomes Secreted by Apoptosis-Resistant Acute Myeloid Leukemia (AML) Blasts Harbor Regulatory Network Proteins Potentially Involved in Antagonism of Apoptosis**. *Mol Cell Proteomics*. 2016 Apr;15(4):1281-98.

Inhibiting Extracellular Vesicle release from breast cancer cells to combat drug resistance (on-going)

Name Collaborators: **Dr. Michiel Pegtel (Dept. Pathology), Dr. Bart Westerman (Dept. Neurosurgery)**

Phosphoproteomics analyses of preclinical models to unravel signaling pathways involved in extracellular vesicle release

- **KWF High Risk Project 2018-11308**, PI Pegtel, coPIs Westerman and Jimenez

Other exosome proteomics publications with Pegtel:

- Verweij FJ, Bebelman MP, Jimenez CR, Garcia-Vallejo JJ, Janssen H, Neefjes J, Knol JC, de Goeij-de Haas R, Piersma SR, Baglio SR, Verhage M, Middeldorp JM, Zomer A, van Rheenen J, Coppolino MG, Hurbain I, Raposo G, Smit MJ, Toonen RFG, van Niel G, Pegtel DM. Quantifying exosome secretion from single cells reveals a modulatory role for GPCR signaling. J Cell Biol. 2018 Mar 5;217(3):1129-1142.
- Baglio SR, van Eijndhoven MA, Koppers-Lalic D, Berenguer J, Lougheed SM, Gibbs S, Léveillé N, Rinkel RN, Hopmans ES, Swaminathan S, Verkuijlen SA, Scheffer GL, van Kuppeveld FJ, de Gruijl TD, Bultink IE, Jordanova ES, Hackenberg M, Piersma SR, Knol JC, Voskuyl AE, Wurdinger T, Jiménez CR, Middeldorp JM, Pegtel DM. Sensing of latent EBV infection through exosomal transfer of 5'pppRNA. Proc Natl Acad Sci U S A. 2016 Feb 2;113:E587-96.
- Verweij FJ, de Heus C, Kroeze S, Cai H, Kieff E, Piersma SR, Jimenez CR, Middeldorp JM, Pegtel DM. Exosomal sorting of the viral oncoprotein LMP1 is restrained by TRAF2 association at signalling endosomes. J Extracell Vesicles. 2015 Apr 10;4:26334.

The Molecular Signalling Pathways of Folliculin (FLCN): a Tumor Suppressor in Birt-Hogg Dubé Hereditary Kidney Cancer (on-going)

Name Collaborator: **Dr. Rob Wolthuis (Clinical Genetics)**

Proteomics and bioinformatics analyses of isogenic cell model made folliculin knock-out with CRISPR-cas

- Joint PhD student supported by **CCA/VUmc** funding to the Dept. Clinical Genetics

Manuscript in prep.:

- Glykofridis IE, et al. **Signaling pathway linked to loss of FLCN in renal cells**
- Glykofridis IE, et al. **Cancer cell secretome and exosome linked to loss of FLCN in renal cells**

Publication:

- Glykofridis IE, Knol JC, Balk JA, Westland D, Pham TV, Piersma SR, Lougheed SM, Derakhshan S, Veen P, Rooimans MA, van Mil SE, Böttger F, Poddighe PJ, van de Beek I, Drost J, Zwartkruis FJ, de Menezes RX, Meijers-Heijboer HE, Houweling AC, Jimenez CR, Wolthuis RM**. Loss of FLCN-FNIP1/2 induces a non-canonical interferon response in human renal tubular epithelial cells**. Elife. 2021 Jan 18;10:e61630.

Identification of biomarkers by whole-genome sequencing and phospho-proteomics to predict responses to high-precision cancer medicines in T-cell acute lymphoblastic leukemia (on-going)

Name Collaborator: **Dr. Jules Meijerink (Prinses Maxima)**

Phosphoproteomics analyses of genomically characterized T-ALL samples for discovery of hyper-activated kinases as novel drug targets

- Joint PhD student Valentina Cordo on a **KWF project 2016-10355** (PI Meijerink, coPI Jimenez)

Manuscript in prep.:

- Cordo et al. **Phosphotyrosine-based phosphoproteomics of a panel tALL cell lines reveals oncogenic signaling and hyperactive tyrosine kinases as targets for treatment**

* Improving clinical management of colon cancer through CONNECTION, a nation-wide Colon Cancer Registry and Stratification effort (on-going)

Name Collaborators: **Prof.dr. Jan Paul Medema (AMC), Prof.dr. Jan Ijzermans (ErasmusMC), Prof.dr. Koopmans (UMCU), Prof.dr. Van Krieken (Radboud MC)**

Contribution: Identification of protein biomarkers for colorectal cancer consensus subtypes that have different prognosis and potentially also different treatment response

- **KWF/Alpe d'Huzes consortium UvA2013-6331** (PI JP Medema, coPIs Ijzermans, Koopmans, Jimenez, Van Krieken)
- Manuscript in prep.

Publication:

- van den Berg I, van de Weerd S, Roodhart JML, Vink GR, van den Braak RRJC, Jimenez CR, Elias SG, van Vliet D, Koelink M, Hong E, van Grevenstein WMU, van Oijen MGH, Beets-Tan RGH, van Krieken JHJM, IJzermans JNM, Medema JP, Koopman M; **CONNECTION-study group. Improving clinical management of colon cancer through CONNECTION, a nation-wide colon cancer registry and stratification effort (CONNECTION II trial): rationale and protocol of a single arm intervention study.** BMC Cancer. 2020 Aug 18;20(1):776.

* Unravelling signaling pathways involved in colorectal adenoma-to-carcinoma progression (completed in 2019, analyses on-going)

Name Collaborators: **Dr. Beatrix Carvalho (NKI), Prof.dr. Gerrit A Meijer (NKI)**

(Phospho)proteomics analyses of patient material that was selected from the biobank by my collaborators based on pathological and genomic selection criteria.

- Joint post-doc S. de Kemp working on the project that written jointly by Carvalho and Jimenez and that was funded by the KWF: **KWF VU2014-6813** (PI Carvalho (NKI), coPIs Jimenez, Meijer).
- Manuscript in prep.

* Tumor-specific protein biomarkers for early detection of colorectal cancer

(completed in 2019)

Name Collaborators: **Dr. Remond JA Fijneman, Prof.dr. Gerrit A Meijer (NKI)**

Proteogenomics analyses of patient material that was selected from several biobanks by my collaborators, based on pathological and genomic selection criteria by joint PhD student.

- **KWF VU2014-6025** (PI Fijneman, coPIs Jimenez, Meijer)

Publications

- Komor MA, de Wit M, van den Berg J, Martens de Kemp SR, Delis-van Diemen PM, Bolijn AS, Tijssen M, Schelfhorst T, Piersma SR, Chiasserini D, Sanders J, Rausch C, Hoogstrate Y, Stubbs AP, de Jong M, Jenster G, Carvalho B, Meijer GA, Jimenez CR, Fijneman RJA; NGS-ProToCol Consortium. **Molecular characterization of colorectal adenomas reveals POFUT1 as a candidate driver of tumor progression**. Int J Cancer. 2020 Apr 1;146(7):1979-1992.
- Komor MA, Bosch LJ, Bounova G, Bolijn AS, van-Diemen PD, Rausch C, Hoogstrate Y, Stubbs AP, de Jong M, Jenster G, van Grieken NC, Carvalho B, Wessels LF, Jimenez CR, Fijneman RJ, Meijer GA; NGS-ProToCol Consortium. **Consensus molecular subtypes classification of colorectal adenomas.** J Pathol. 2018 Jul 3.
- Komor MA, Pham TV, Hiemstra AC, Piersma SR, Bolijn AS, Schelfhorst T, Delis-van Diemen PM, Tijssen M, Sebra RP, Ashby M, Meijer GA, Jimenez CR, Fijneman RJA. **Identification of Differentially Expressed Splice Variants by the Proteogenomic Pipeline Splicify.** Mol Cell Proteomics. 2017 Oct;16(10):1850-1863.

* Improved early detection of colorectal cancer

(on-going but role proteomics has ended in 2018)

Name Collaborator: ***Prof.dr. Gerrit Meijer (NKI)***

Identification of protein biomarkers in stool of control subjects and patients with colorectal adenomas and carcinomas for development of improved screening markers.

- This project started in 2009 and was funded by the Center for Translation Molecular Medicine (CTMM) projects Decrease Colorectal Cancer Death (**DeCoDe**) and **CRC Bioscreen**, in which we identified and validated novel stool protein markers for colorectal cancer screening. These markers are now being prospectively validated in the context of a KWF-AACR SU2C project (**MEDDOCC**, PIs Meijer and Velculescu)
- **Patent 2008707** "Biomarkers", a screening method for the diagnosis of colorectal cancer comprising identifying protein markers in (stool) samples, where the markers are selected from a large group of protein biomarkers known to be over-expressed in cases of colorectal cancer (priority date: 26th April 2012).
- **Patent WO2010119362** "Protein-based methods and compositions for the diagnosis of colorectal adenocarcinoma" (priority date: 7th of April in 2009)

Publications

- Komor MA, Bosch LJ, Coupé VM, Rausch C, Pham TV, Piersma SR, Mongera S, Mulder CJ, Dekker E, Kuipers EJ, van de Wiel MA, Carvalho B, Fijneman RJ, Jimenez CR, Meijer GA, de Wit M. **Proteins in stool as biomarkers for non-invasive detection of colorectal adenomas with high risk of progression**. J Pathol. 2020 Mar;250(3):288-298.
- Bosch LJW, de Wit M, Pham TV, Coupé VMH, Hiemstra AC, Piersma SR, Oudgenoeg G, Scheffer GL, Mongera S, Sive Droste JT, Oort FA, van Turenhout ST, Larbi IB, Louwagie J, van Criekinge W, van der Hulst RWM, Mulder CJJ, Carvalho B, Fijneman RJA, **Jimenez CR***, Meijer GA*. **Novel Stool-Based Protein Biomarkers for Improved Colorectal Cancer Screening: A Case-Control Study**. Ann Intern Med. 2017 Dec 19;167(12):855-866. **Shared Senior Authors*

- den Uil SH, de Wit M, Slebos RJC, Delis-van Diemen PM, Sanders J, Piersma SR, Pham TV, Coupé VMH, Bril H, Stockmann HBAC, Jimenez CR, Meijer GA, Fijneman RJA. **Quantitative analysis of CDX2 protein expression improves its clinical utility as a prognostic biomarker in stage II and III colon cancer.** Eur J Cancer. 2021 Feb;144:91-100.

Optimized high-order low-dose drug mixtures boost selectivity and efficacy of anti-cancer targeted combination treatments (completed)

Name Collaborators: **Prof.dr. Arjan Griffioen (dept. Medical Oncology), Dr. Patrycja Nowak-Sliwinska (Austria)**

Phoshoproteomics and bioinformatics analyses of cancer cell lines and correlation of baseline data to response to drug combinations

Publications:

- van Beijnum JR, Weiss A, Berndsen RH, Wong TJ, Reckman LC, Piersma SR, Zoetemelk M, de Haas R, Dormond O, Bex A, Henneman AA, Jimenez CR, Griffioen AW, Nowak-Sliwinska P. **Integrating Phenotypic Search and Phosphoproteomic Profiling of Active Kinases for Optimization of Drug Mixtures for RCC Treatment**. Cancers (Basel). 2020 Sep 21;12(9):2697.
- Zoetemelk M, Ramzy GM, Rausch M, Koessler T, van Beijnum JR, Weiss A, Mieville V, Piersma SR, de Haas RR, Delucinge-Vivier C, Andres A, Toso C, Henneman AA, Ragusa S, Petrova TV, Docquier M, McKee TA, Jimenez CR, Daali Y, Griffioen AW, Rubbia-Brandt L, Dietrich PY, Nowak-Sliwinska P. **Optimized low-dose combinatorial drug treatment boosts selectivity and efficacy of colorectal carcinoma treatment**. Mol Oncol. 2020 Oct 5;14(11):2894–919.
- Rausch M, Weiss A, Zoetemelk M, Piersma SR, Jimenez CR, van Beijnum JR, Nowak-Sliwinska P. **Optimized Combination of HDACI and TKI Efficiently Inhibits Metabolic Activity in Renal Cell Carcinoma and Overcomes Sunitinib Resistance**. Cancers (Basel). 2020 Oct 28;12(11):3172.

Glycans to reprogram the immune response (completed)

Name Collaborators: **Dr. Sandra. Van Vliet (MCBI), Prof.dr. Yvette van Kooyk (MCBI)**

Phosphoproteomics, proteomics and bioinformatics analyses of sugar-stimulated immune cells.

- Contribution to one study of PhD student Eveline Li of the Dept. MCBI.

Manuscript in prep.:

- R.J. Eveline Li[1], J. Ernesto Rodriguez-Camejo[1], Hakan Kalay[1], Anouk Zaal[1], Connie R. Jimenez[2], Sander R. Piersma[2], Thang V. Pham[2], Richard R. de Goeij- de Haas[2], Sandra J.van Vliet[1], Yvette van Kooyk[1*] M **Quantitative phosphoproteomic analysis reveals specific dendritic cell STAT signaling after α2,3-linked sialic acid ligand binding.**

Mechanisms in the cellular defense against oxidative stress (completed)

Name Collaborators: **Dr. Josephine Dorsman and Prof.dr. H. Joenje (Clinical Genetics)**

Proteomics and bioinformatics analyses of hyperoxia-resistant and sensitive cell lines to identify novel proteins and cellular mechanism(s) involved in the defense against oxidative stress.

- Contribution to 2 thesis chapters of PhD student Monique Corbin of the Dept. Clinical Genetics.

Thesis chapters:

- M.V Corbin[1], D.A.P Rockx[1], T.V. Pham[2], S.R. Piersma[2], J.C. Knol[2], H. Joenje[1], C.R. Jimenez[2*], J.C.Dorsman[1*] **Loss of NARFL function deregulates iron regulatory and cohesin complex cleavage proteins under hyperoxia-induced oxidative stress**

- M.V Corbin[1]; D.A.P Rockx[1]; T.V. Pham[2]; S.R. Piersma[2]; J.C. Knol[2]; H. Joenje[1]; C.R. Jimenez[2*]; J.C.Dorsman[1*] **Protein biomarkers with potential relevenace for cellular resistance against oxidative stress**

Cancer cell communication via extracellular vesicles (completed)

Name Collaborator: **Prof.dr. Jacco van Rheenen (NKI)**

Proteomics of melanoma tumor tissue and EVs shed *in vivo* by two clones of melanoma (B16) tumors with distinct metastatic potential and data analysis to understand the differential behaviour.

Publication:

- Steenbeek SC, Pham TV, de Ligt J, Zomer A, Knol JC, Piersma SR, Schelfhorst T, Huisjes R, Schiffelers RM, Cuppen E, Jimenez CR*, van Rheenen J*. **Cancer cells copy migratory behavior and exchange signaling networks via extracellular vesicles**. EMBO J. 2018 Jun 14. pii: e8357. [Epub ahead of print. PMID: 29907695 Shared senior authors.

Exploration of transiently secreted factor that enhances immune reconstitution (completed)

Name Collaborator: **Dr. Davide Chiasserini and Dr. A Velardi (University of Perugia, Perugia, Italy)**

Proteomics of conditioned media derived from stable isotope labelled mice and human cells

Submitted manuscript:

- Loredana Ruggeri, Elena Urbani, Davide Chiasserini, Federica Susta, Pier Luigi Orvietani, Emanuela Burchielli, Sara Ciardelli, Maria Speranza Massei, Stefano Bruscoli, Sander R. Piersma, Dunia Ramarli, Luciano Binaglia, Connie R. Jimenez, Georg A. Hollander and Andrea Velardi. **Natural killer cells trigger beta-2-microglobulin production to enhance immune reconstitution.**

Platelet proteomics for non-invasive cancer detection (completed)

Name Collaborator: **Prof.dr. Arjan Griffioen (Medical Oncology), Prof.dr. MGA Oude Egbrink (Maastricht UMC)**

Publication:

- Sabrkhany S, Kuijpers MJE, Knol JC, Olde Damink SWM, Dingemans AC, Verheul HM, Piersma SR, Pham TV, Griffioen AW, Oude Egbrink MGA, Jimenez CR. **Exploration of the platelet proteome in patients with early-stage cancer.** J Proteomics. 2018 Apr 15;177:65-74.

Manuscripts related to OncoProteomics methodology projects last 5 years

Manuscripts in prep:

- Thang V Pham, Frank Rolfs, Jim Termeulen, Alex A Henneman, Sander R Piersma, Connie R Jimenez **Assessment of quantitation and statistical methods for DIA mass spectrometry-based proteomics data**

Submitted manuscripts:

- Frank Rolfs, Sander R. Piersma, Mariana Paes Dias, Jos Jonkers,* Connie R. Jimenez. **Feasibility of phosphoproteomics on leftover samples after RNA extraction with guanidinium thiocyanate** In revision for Mol. Cell. Prot.

Publications:

Zhu T, Zhu Y, Xuan Y, Gao H, Cai X, Piersma SR, Pham TV, Schelfhorst T, Haas RRGD, Bijnsdorp IV, Sun R, Yue L, Ruan G, Zhang Q, Hu M, Zhou Y, Van Houdt WJ, Le Large TYS, Cloos J, Wojtuszkiewicz A, Koppers-Lalic D, Böttger F, Scheepbouwer C, Brakenhoff RH, van Leenders GJLH, Ijzermans JNM, Martens JWM, Steenbergen RDM, Grieken NC, Selvarajan S, Mantoo S, Lee SS, Yeow SJY, Alkaff SMF, Xiang N, Sun Y, Yi X, Dai S, Liu W, Lu T, Wu Z, Liang X, Wang M, Shao Y, Zheng X, Xu K, Yang Q, Meng Y, Lu C, Zhu J, Zheng J, Wang B, Lou S, Dai Y, Xu C, Yu C, Ying H, Lim TK, Wu J, Gao X, Luan Z, Teng X, Wu P, Huang S, Tao Z, Iyer NG, Zhou S, Shao W, Lam H, Ma D, Ji J, Kon OL, Zheng S, Aebersold R, Jimenez CR, Guo T. **DPHL: A DIA Pan-human Protein Mass Spectrometry Library for Robust Biomarker Discovery.** Genomics Proteomics Bioinformatics. 2020 Apr;18(2):104-119.

Xuan Y, Bateman NW, Gallien S, Goetze S, Zhou Y, Navarro P, Hu M, Parikh N, Hood BL, Conrads KA, Loosse C, Kitata RB, Piersma SR, Chiasserini D, Zhu H, Hou G, Tahir M, Macklin A, Khoo A, Sun X, Crossett B, Sickmann A, Chen YJ, Jimenez CR, Zhou H, Liu S, Larsen MR, Kislinger T, Chen Z, Parker BL, Cordwell SJ, Wollscheid B, Conrads TP. **Standardization and harmonization of distributed multi-center proteotype analysis supporting precision medicine studies.** Nat Commun. 2020 Oct 16;11(1):5248.

Pham TV, Henneman AA, Jimenez CR. **iq: an R package to estimate relative protein abundances from ion quantification in DIA-MS-based proteomics**. Bioinformatics. 2020 Jan 7. pii: btz961.

Beekhof R, van Alphen C, Henneman AA, Knol JC, Pham TV, Rolfs F, Labots M, Henneberry E, Le Large TY, de Haas RR, Piersma SR, Vurchio V, Bertotti A, Trusolino L, Verheul HM, Jimenez CR. **INKA, an integrative data analysis pipeline for phosphoproteomic inference of active kinases.** Mol Syst Biol. 2019 Apr 12;15(4):e8250.

Labots M, van der Mijn JC, Beekhof R, Piersma SR, de Goeij-de Haas RR, Pham TV, Knol JC, Dekker H, van Grieken NCT, Verheul HMW, Jiménez CR. **Phosphotyrosine-based-phosphoproteomics scaled-down to biopsy level for analysis of individual tumor biology and treatment selection**. J Proteomics. 2017 Jun 6;162:99-107.

Pham TV, Jimenez CR. **Simulated linear test applied to quantitative proteomics.** Bioinformatics. 2016 Sep 1;32(17):i702-i709.

Knol JC, de Reus I, Schelfhorst T, Beekhof R, de Wit M, Piersma SR, Pham TV, Smit EF, Verheul HMW, Jiménez CR. **Peptide-mediated 'miniprep' isolation of extracellular vesicles is suitable for high throughput proteomics**. EuPA Open Proteom. 2016 Feb 22;11:11-15.

Bijnsdorp IV, Maxouri O, Kardar A, Schelfhorst T, Piersma SR, Pham TV, Vis A, van Moorselaar RJ, Jimenez CR. **Feasibility of urinary extracellular vesicle proteome profiling using a robust and simple, clinically applicable isolation method.** J Extracell Vesicles. 2017 Apr 28;6(1):1313091.

van der Mijn JC, Labots M, Piersma SR, Pham TV, Knol JC, Broxterman HJ, Verheul HM, Jiménez CR. **Evaluation of different phospho-tyrosine antibodies for label-free phosphoproteomics.** J Proteomics. 2015 Sep 8;127(Pt B):259-63.

Piersma SR, Knol JC, de Reus I, Labots M, Sampadi BK, Pham TV, Ishihama Y, Verheul HM, Jimenez CR. **Feasibility of label-free phosphoproteomics and application to base-line signaling of colorectal cancer cell lines.** J Proteomics. 2015 Sep 8;127(Pt B):247-58.

Miscellaneous publications (smaller collaborations/ core facility) last 5 years

AMSTERDAM UMC

Dept. Medical Oncology

Poel D, Boyd LNC, Beekhof R, Schelfhorst T, Pham TV, Piersma SR, Knol JC, Jimenez CR, Verheul HMW, Buffart TE. **Proteomic Analysis of miR-195 and miR-497 Replacement Reveals Potential Candidates that Increase Sensitivity to Oxaliplatin in MSI/P53wt Colorectal Cancer Cells**. Cells. 2019 Sep 19;8(9). pii: E1111.

López González M, Oosterhoff D, Lindenberg JJ, Milenova I, Lougheed SM, Martiáñez T, Dekker H, Quixabeira DCA, Hangalapura B, Joore J, Piersma SR, Cervera-Carrascon V, Santos JM, Scheper RJ, Verheul HMW, Jiménez CR, Van De Ven R, Hemminki A, Van Beusechem VW, De Gruijl TD. **Constitutively active GSK3β as a means to bolster dendritic cell functionality in the face of tumour-mediated immune suppression.** Oncoimmunology. 2019 Jul 19;8(10):e1631119.

Labots M, Gotink KJ, Dekker H, Azijli K, van der Mijn JC, Huijts CM, Piersma SR, Jiménez CR, Verheul HM. **Evaluation of a tyrosine kinase peptide microarray for tyrosine kinase inhibitor therapy selection in cancer.** Exp Mol Med. 2016 Dec 16;48(12):e279.

van Linde ME, van der Mijn JC, Pham TV, Knol JC, Wedekind LE, Hovinga KE, Aliaga ES, Buter J, Jimenez CR, Reijneveld JC, Verheul HM. **Evaluation of potential circulating biomarkers for prediction of response to chemoradiation in patients with glioblastoma.** J Neurooncol. 2016 Sep;129(2):221-30.

Rovithi M, Lind JS, Pham TV, Voortman J, Knol JC, Verheul HM, Smit EF, Jimenez CR. **Response and toxicity prediction by MALDI-TOF-MS serum peptide profiling in patients with non-small cell lung cancer.** Proteomics Clin Appl. 2016 Jul;10(7):743-9.

Dept. of Otolaryngology-Head and Neck Surgery

Nagel R, Stigter-van Walsum M, Buijze M, van den Berg J, van der Meulen IH, Hodzic J, Piersma SR, Pham TV, Jiménez CR, van Beusechem VW, Brakenhoff RH. **Genome-wide siRNA Screen Identifies the Radiosensitizing Effect of Downregulation of MASTL and FOXM1 in NSCLC.** Mol Cancer Ther. 2015 Jun;14(6):1434-44.

Dept. Clinical Genetics

van Dijk FS, Semler O, Etich J, Köhler A, Jimenez-Estrada JA, Bravenboer N, Claeys L, Riesebos E, Gegic S, Piersma SR, Jimenez CR, Waisfisz Q, Flores CL, Nevado J, Harsevoort AJ, Janus GJM, Franken AAM, van der Sar AM, Meijers-Heijboer H, Heath KE, Lapunzina P, Nikkels PGJ, Santen GWE, Nüchel J, Plomann M, Wagener R, Rehberg M, Hoyer-Kuhn H, Eekhoff EMW, Pals G, Mörgelin M, Newstead S, Wilson BT, Ruiz-Perez VL, Maugeri A, Netzer C, Zaucke F, Micha D. **Interaction between KDELR2 and HSP47 as a Key Determinant in Osteogenesis Imperfecta Caused by Bi-allelic Variants in KDELR2.** Am J Hum Genet. 2020 Nov 5;107(5):989-999.

Dept. Microbiology

Phan TH, van Leeuwen LM, Kuijl C, Ummels R, van Stempvoort G, Rubio-Canalejas A, Piersma SR, Jiménez CR, van der Sar AM, Houben ENG, Bitter W. **EspH is a hypervirulence factor for Mycobacterium marinum and essential for the secretion of the ESX-1 substrates EspE and EspF.** PLoS Pathog. 2018 Aug 13;14(8):e1007247.

Ates LS, Dippenaar A, Ummels R, Piersma SR, van der Woude AD, van der Kuij K, Le Chevalier F, Mata-Espinosa D, Barrios-Payán J, Marquina-Castillo B, Guapillo C, Jiménez CR, Pain A, Houben ENG,

Warren RM, Brosch R, Hernández-Pando R, Bitter W. **Mutations in ppe38 block PE_PGRS secretion and increase virulence of Mycobacterium tuberculosis**. Nat Microbiol. 2018 Feb;3(2):181-188.

van Winden VJ, Ummels R, Piersma SR, Jiménez CR, Korotkov KV, Bitter W, Houben EN. **Mycosins Are Required for the Stabilization of the ESX-1 and ESX-5 Type VII Secretion Membrane Complexes.** mBio. 2016 Oct 18;7(5). pii: e01471-16.

Ates LS, Ummels R, Commandeur S, van de Weerd R, Sparrius M, Weerdenburg E, Alber M, Kalscheuer R, Piersma SR, Abdallah AM, Abd El Ghany M, Abdel-Haleem AM, Pain A, Jiménez CR, Bitter W, Houben EN. **Essential Role of the ESX-5 Secretion System in Outer Membrane Permeability of Pathogenic Mycobacteria.** PLoS Genet. 2015 May 4;11(5):e1005190.

Dept. Physiology

Schuldt M, Pei J, Harakalova M, Dorsch LM, Schlossarek S, Mokry M, Knol JC, Pham TV, Schelfhorst T, Piersma SR, Dos Remedios C, Dalinghaus M, Michels M, Asselbergs FW, Moutin MJ, Carrier L, Jimenez CR, van der Velden J, Kuster DWD. **Proteomic and Functional Studies Reveal Detyrosinated Tubulin as Treatment Target in Sarcomere Mutation-Induced Hypertrophic Cardiomyopathy**. Circ Heart Fail. 2021 Jan;14(1):e007022.

Turaihi AH, Serné EH, Molthoff CF, Koning JJ, Knol J, Niessen HW, Jose Th Goumans M, van Poelgeest EM, Yudkin JS, Smulders YM, Jimenez CR, van Hinsbergh VW, Eringa EC. **Perivascular Adipose Tissue Controls Insulin-Stimulated Perfusion, Mitochondrial Protein Expression and Glucose Uptake in Muscle Through Adipomuscular Arterioles.** Diabetes. 2020 Jan 31. pii: db181066.

Dept. Clinical Chemistry

van Steenoven I, Koel-Simmelink MJA, Vergouw LJM, Tijms BM, Piersma SR, Pham TV, Bridel C, Ferri GL, Cocco C, Noli B, Worley PF, Xiao MF, Xu D, Oeckl P, Otto M, van der Flier WM, de Jong FJ, Jimenez CR, Lemstra AW, Teunissen CE. **Identification of novel cerebrospinal fluid biomarker candidates for dementia with Lewy bodies: a proteomic approach**. Mol Neurodegener. 2020 Jun 18;15(1):36. doi: 10.1186/s13024-020-00388-2. PMID: 32552841; PMCID: PMC7301448.

Bridel C, Koel-Simmelink MJA, Peferoen L, Derada Troletti C, Durieux S, Gorter R, Nutma E, Gami P, Iacobaeus E, Brundin L, Kuhle J, Vrenken H, Killestein J, Piersma SR, Pham TV, De Vries HE, Amor S, Jimenez CR, Teunissen CE. **Brain endothelial cell expression of SPARCL-1 is specific to chronic multiple sclerosis lesions and is regulated by inflammatory mediators in vitro.** Neuropathol Appl Neurobiol. 2018 Jun;44(4):404-416.

Teunissen CE, Elias N, Koel-Simmelink MJ, Durieux-Lu S, Malekzadeh A, Pham TV, Piersma SR, Beccari T, Meeter LH, Dopper EG, van Swieten JC, Jimenez CR, Pijnenburg YA. **Novel diagnostic cerebrospinal fluid biomarkers for pathologic subtypes of frontotemporal dementia identified by proteomics.** Alzheimers Dement (Amst). 2016 Jan 19;2:86-94.

Del Campo Milan M, Zuroff L, Jimenez CR, Scheltens P, Teunissen CE. **Can agrin cerebrospinal fluid concentration be used as an early biomarker for Alzheimer's disease?** Alzheimers Dement (Amst). 2015 Mar 29;1(1):75-80.

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Castillo J, Knol JC, Korver CM, Piersma SR, Pham TV, de Goeij-de Haas RR, van Pelt AMM, Jimenez CR, Jansen BJH. Human Testis **Phosphoproteome Reveals Kinases as Potential Targets in Spermatogenesis and Testicular Cancer**. Mol Cell Proteomics. 2019 Mar 15;18(Suppl 1):S132-S144.

Schouten M, Bielefeld P, Fratantoni SA, Hubens CJ, Piersma SR, Pham TV, Voskuyl RA, Lucassen PJ, Jimenez CR, Fitzsimons CP. **Multi-omics profile of the mouse dentate gyrus after kainic acid-induced status epilepticus.** Sci Data. 2016 Aug 16;3:160068.

EXTERN

Spain: González-Alonso P, Zazo S, Martín-Aparicio E, Luque M, Chamizo C, Sanz-Álvarez M, Minguez P, Gómez-López G, Cristóbal I, Caramés C, García-Foncillas J, Eroles P, Lluch A, Arpí O, Rovira A, Albanell J, Piersma SR, Jimenez CR, Madoz-Gúrpide J, Rojo F. **The Hippo Pathway Transducers YAP1/TEAD Induce Acquired Resistance to Trastuzumab in HER2-Positive Breast Cancer**. Cancers (Basel). 2020 Apr 29;12(5):1108.

UMCU Stokman MF, Bijnsdorp IV, Schelfhorst T, Pham TV, Piersma SR, Knol JC, Giles RH, Bongers EMHF, Knoers NVAM, Lilien MR, Jiménez CR, Renkema KY. **Changes in the urinary extracellular vesicle proteome are associated with nephronophthisis-related ciliopathies.** J Proteomics. 2019 Feb 10;192:27-36.

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Other experiments performed/ planned/ in progress with:

Linda Smit (Hematology); Richard Groen (Hematology); Jacqueline Cloos (Hematology); Ruud Brakenhoff (Otolaryngology); Josephine Dorsman (Clinical Genetics); Job de Lange (Clinicsl Genetics); Marjolein van Egmond (MCBI); Michiel Pegtel (Pathology); Jolanda van den Velden (Physiology); Peter Hordijk (Physiology); Robert Szulcek (Physiology); Tanja Gruijl, Victor van Beusechem (Medical Oncology); Charlotte Teunissen (Clinical Chemistry); Esther Hulleman (Pediatric Oncology); Wilbert Bitter (Medical Microbiology); Oudeelferink (AMC); Versteeg group (AMC); Jan Paul Medema (AMC); Hanneke van Laarhoven (AMC); Maurice Aalders (AMC); Marthe Minderman (AMC); Connie Bezzina (AMC); J. deGroot (E Meulendijks) (AMC); Erik Reits (AMC); Martine Smit (VU); Ronald van Kesteren (VU); Edith Houben (VU); Winan van Houdt (NKI); Katrien Keune (Rijksmuseum); Purificacion Munoz (Spain); Madiha Mumtaz (Pakistan); Mohan Shankar (India).

What do our collaborators say about the OncoProteomics Laboratory?

Dr. Jacqueline Cloos, Dept. Hematology, collaborator since 2012:

"De afdeling Hematologie heeft samen met het OPL een aantal mooie studies lopen waar al heel interessante data uit zijn gekomen. Kroon op het werk is een artikel in Molecular and Cellular Proteomics waarin we laten zien dat leukemiecellen blaasjes uitscheiden met daarin met name eiwitten betrokken bij splicing. In een ander succesvol project karakteriseren we specifiek het tyrosine fosfoproteoom van verschillende leukemiecellen om aan de hand van deze profielen de juiste kinase remmers te selecteren voor het behandelen van de patiënt. Naast de technische support bij de experimenten krijgen we gelukkig ook veel support voor de data analyses om de biologische significantie te vinden in de grote datasets.
Omdat de (gefosforyleerde) eiwitten veel zeggen over de functionele processen in de cel is proteomics een mooie aanvulling op de genomics en transcriptomics en zullen we ook in de toekomst nog veel gebruik maken van deze faciliteit."

Dr. Linda Smit, Dept. Hematology, collaborator since 2014:

Mijn onderzoeksgroep is op zoek naar eiwitten die gebruikt kunnen worden als therapie doelwitten en de terugkeer van leukemie kunnen voorkomen. De proteomics faciliteit geleid door Connie Jimenez heeft al een **fantastische bijdrage** geleverd aan dit onderzoek door proteomics te doen op de cellen die verantwoordelijk zijn voor de leukemie terugkeer. **We hebben op deze manier al verschillende eiwitten geïdentificeerd die mogelijk gaan leiden tot een nieuwe therapie die de overleving van leukemie patiënten gaat verbeteren**.

Dr. Michiel Pegtel, Dept. Pathology, collaborator since 2007:

De Exosomens research group (ERG), is een multidisciplinaire onderzoeksgroep van het VUmc die internationaal bekend staat om baanbrekend onderzoek naar exosomen en de rol die deze nanoscopische vetblaasjes spelen in kanker en autoimmuniteit. **Sind de start van dit laboratoriumonderzoek zijn met behulp van massaspectometrie en innovatieve data-analyse methodes met behulp van en ontwikkeld door het OPL verschillende nieuwe fundamentele inzichten verkregen**. Recent heeft dit geleid tot een publicatie in **PNAS** waarin werd aangetoond met massaspectometrie dat RNA-bindende eiwitten een inhiberende rol spelen in ontstekingen veroorzaakt door uitgescheiden RNA moleculen. Tevens is met behulp van de kwantitatieve analyse methode van het OPL ontdekt dat druggable 'membraan fusie' eiwitten oncogenese bevorderen omdate deze ongecontroleerde exosomen productie in kankercellen 'aan' zetten. Het is de verwachting dat door middel van **nieuwe isolatietechnieken mede ontwikkeld door het ERG in combinatie met gevoelige eiwit detectie technieken van het OPL nieuwe diagnostische testen** kunnen worden ontwikkeld voor kanker en auto-immuniteit met een superieure sensitiviteit en specificiteit.

Dr. Irene Bijnsdorp, Dept. Urology, collaborator since 2012:

Research of the Dept. of Urology focusses on protein marker identification for detection and stratification of prostate cancer patients into risks groups. To this end we analyze small extracellular vesicles (exosomes) that have emerged as biomarker-rich treasure troves. Together with dr. C. Jimenez of the OPL, we profiled the proteome of urinary exosomes leading to the identification of over 3000 proteins. **This is much more than has been identified before by others** (usually not exceeding 1500 proteins). Initial proof-of-concept proteomics profiling led to the improvement of exosome isolation of urine EVs. Furthermore, after data mapping and **key (bio)statistical support provided by the OPL-group, led to the identification of potential PCa biomarkers**. This work was the basis for the financial support (KWF, Alpe d'Huzes) of a collaborative project together with Prof. Jenster (Erasmus MC) and Prof. Schalken (Radboud UMC). This project will take advantage of the **excellent infrastructure and expertise in exosome-proteomics**(Dr. Jimenez) and it is expected that this project will provide a strong basis for developing a liquid biopsy-based diagnostic/prognostic test for PCa.

Prof. Ruud Brakenhoff, Dept.Otolaryngology-Head&Neck Surgery, collaborator since 2010:

The Tumor Biology lab focuses its research on the diagnosis and treatment of patients with tumors in the upper aerodigestive tract. Using genome-wide siRNA screens we identified a variety of novel molecular targets that might be exploited to improve future therapy protocols, combined with standard first line treatments. One of the major research efforts is to elucidate the molecular pathways these drug targets act in, and using (phospho)proteomics approaches both primary and secondary substrate proteins can be identified, and the effects of inhibitors analyzed. This was recently published for the MASTL protein, a kinase that sensitizes lung cancer cells for radiotherapy (Nagel et al. Mol Cancer Ther 2015). **This work will certainly be followed up for targets and inhibitors being studied, and proteomics and phosphoproteomics are the ideal pipelines for such studies.**

Dr. Josephine Dorsman, Dept. Clinical Genetics, collaborator since 2010:

“Het is goed om in-huis een kOPLoper in protemics te hebben, om nieuwe inzichten & OPLossingen te vinden voor basale en translationale vragen. Ook daadwerkelijk gebeurd in samenwerking: Fanconi & Zuurstof tolerantie ! Omdat het juist de eiwitten in de cel zijn die het werk doen, verwachten wij dat het OPL onderzoek nog veel gaat **OPLeveren** in de toekomst.”

Dr. Rob Wolthuis, Dept. Clinical Genetics, collaborator since 2015:

“In the era of cancer -omics, we see two critical developments: the first one is directed at resolving biological and clinical implications of cancer mutations. Already at an early stage, Connie Jimenez started to address these by effectively exploiting a combination of cancer genomics and proteomics. Secondly, there is an enormous need for new combination therapies that could overcome drug resistance associated with targeted mono-therapies. This absolutely requires advanced molecular pathway analyses and functional kinase studies, which are technically very challenging. The Jimenez lab has generated powerful new assays for rapid phosphoproteomics and links them to state-of-the art bioinformatics, a great combination. **With these expertises in full operation, the lab functions at a state-of-the-art international level now, and has tremenduous value for cancer research at the CCA.** We look forward to continuing our various research lines with the OPL''

Dr. Juan Vallejo, Dept. Molecular Cell Biology & Immunology, collaborator since 2015:

“At the group of Dendritic Cell Immunobiology we focus on the role of glycan-binding receptors on the modulation of immune responses and their potential use as targeting receptors for anti-cancer vaccination. One of the most interestign features of these broad family of receptors is that, besides mediating efficient antigen uptake, they also trigger intracellular signaling that modulatest dendritic cell activation. However, the nature of the signaling events involved in this pathway remains only partly uncovered, and next generation phosphoproteomics will be extremely useful in shedding light on this processes.”

Prof. Wilbert Bitter, Dept. Medical Microbiology, collaborator since 2006:

“The proteomics facility of the OPL has been crucial for our work on the tubercle bacillus. We have generated various secretion mutants and the detailed proteomic analysis of these mutants has shown important new insights in the working of this major pathogen. The high-end equipment and expertise of the OPL researchers in the data processing helped us to place ourselves in the forefront of tuberculosis research. Especially because some of the most important proteins turned out to be extremely challenging to capture by proteomics. This work has resulted in 8 publications including papers in PloS Pathogens and PloS Genetics, as well as in new strategies for vaccine development.”

Prof. Arjan Griffioen, Dept. Medical Oncology, collaborator since 2014:

'The Oncoproteomics Laboratory very successfully assisted several projects that are currently running in the Angiogenesis Laboratory. Proteomics approaches were applied in the search for alternative isoforms of the tumor vascular marker vimentin and for the discovery of diagnostic biomarkers present in cancer patient thrombocytes. The expert collaboration has been efficient, fast

and successful. A future collaborative project will focus on the mechanisms of targeted combination therapy by phophoproteomics.'

Drs. Mariette Labots M.D., Dept. Medical Oncology (clinical staff), collaborator 2012:

Als medisch oncoloog leg ik patiënten met uitgezaaide kanker dagelijks uit hoe targeted therapies werken. En ook dat we op voorhand niet weten of de behandeling wel zal aanslaan, of, dat als deze blijkt te werken, op termijn meestal toch ongevoeligheid zal ontstaan. Vaak vraag ik om toestemming voor het nemen van een tumorbiopt voor onderzoek: omdat we samen met het OPL hard werken aan een (fosfo)eiwittest om in de toekomst te kunnen bepalen welke signaleringsroutes actief zijn in de tumor, om hiermee de meest geschikte behandeling te kunnen selecteren voor een individuele patient.
Zo hebben we in de afgelopen jaren de voor personalized medicine veelbelovende fosfoproteomics-technologie toepasbaar weten te maken op maar een heel klein stukje tumorweefsel van patienten. Dit maakt verdere ontwikkeling van deze technologie voor de klinische praktijk mogelijk. Ik ben er van overtuigd dat (fosfo)proteomics een belangrijke bijdrage zal leveren aan het realiseren van therapieselectie voor individuele patienten.
De samenwerking met het OncoProteomicsLab is inspirerend, snel en biedt mede door de inbedding binnen de afdeling medische oncologie veel mogelijkheden voor translationeel onderzoek. De onderzoeksfocus binnen het OPL-lab naar het toepassen van fosfoproteomics voor personalized medicine is uniek in Nederland. Connie Jimenez weet mede dankzij state-of-the-art apparatuur de snelle ontwikkelingen binnen dit onderzoeksveld bij te houden en neemt hierin ook internationaal een voortrekkende positie in.

Prof. Tanja de Gruijl, Dept. Medical Oncology, collaborator since 2016:

“The immunotherapy lab, in a VUmc/AMC Alliance collaborative project with the lab of Prof. Theo Geijtenbeek, is studying ways in which to optimally leverage autophagy in melanoma, in order to boost T cell immunity in vivo. Together with the Proteomics lab we hope to asess the protein content of differentially generated autophagosomes for their immunogenic potential, both in terms of (neo-)epitopes and immune stimulatory signals.
In addition, in our search for predictive immune biomarker profiles in patients treated with immunotherapies, targeted therapies and even more conventional chemo- or radiotherapies, we hope in future to translate systemic phenotypic immune effector cell subset signatures to (phospho)proteomic signatures, building on the technical know-how and unique expertise of Dr Jiménez and her lab."

Prof. Jan Paul Medema, Lexor, collaborator since 2014:

“One of LEXOR’s research lines focusses on colorectal cancer prognosis and response to therapy. We identified biologically subgroups with highly distinctive gene expression patterns and clinical features, which includes a subtype with dismal prognosis. In collaboration with the OPL we are currently unravelling the proteome complement of these CRC transcriptome-based subtypes. We obtained promising, in-depth proteome data of the AMC colon tumors that may pave the way to novel immunohistochemical test. Together with also ErasmusMC, UMCU and RadboudMC, we obtained funding from KWF/ Alpe d’Huzes that will enable us to expand the CRC proteome dataset and to translate these findings into a clinically applicable test.”

Dr. Charlotte Teunissen, Dept. Clinical Chemistry, collaborator since 2005:

“Het OPL heeft een grondige en zeer betrouwbare workflow opgezet voor liquor proteomics. Hiermee hebben we verschillende studies kunnen doen, waardoor we inzicht gekregen hebben in het liquor proteome, en nieuwe kandidaat biomarkers ontdekt hebben. Hierdoor hebben we zowel diagnostische en mechanistisch/pathologische vervolgstudies kunnen uitvoeren.”

Prof. dr. Jolanda van der Velden, Dept. Physiology, collaborator since 2015:

Prof. Jolanda van der Velden, Dr. Diederik Kuster and Maike Schuldt study determinants of disease

progression in genetic cardiac disease within a reserach consortium, which is funded by the Netherlnads Heart Foundation (CVON-DOSIS):
The proteomics facility of the OPL is key in identifying cellular pathways that are centrally involved in disease progression in hypertrophic cardiomyopathy. Proteomics analysis has been performed in cardiac tissue samples from 60 genotyped and clinically well-characterized patients. We expect to report our results in a joint publication. The identified disease modifiers will be tested in functional assays to establish their exact role in cardiac disease.

Prof. Gerrit Meijer, Dr. Remond Fijneman, NKI, collaborator since 2006:

"10 years of OPL = 10 years of collaborative and successful CRC research: congratulations! The OPL turned in-depth protein profiling of colorectal tumors into a reality, which added a new dimension to our research. Major achievements: The collaborative research with OPL has yielded many protein biomarkers, and has boosted research for early detection of CRC. Near future work: The OPL enables antibody-independent validation of protein biomarkers, thereby bridging the gap between biomarker discovery and assay development for clinical applications. The pleasant atmosphere around the OPL offers an inviting environment for Master students, PhD students, and postdocs to learn what proteomics is about."

Prof. Onno Kranenburg, UMCU, collaborator since 2007:

"The Kranenburg research group aims to devise novel therapeutic strategies aiming to prevent and effectively treat metastasis in CRC, in part by targeting cancer stem cells. The OPL has been instrumental in elucidating drug resistance mechanisms in CRC stem cells, which has resulted in the publication of 6 co-authored papers in high-impact journals in the cancer and proteomics domains. We have recently further identified novel targets for therapy that drive tumor growth and metastasis in the most aggressive (mesenchymal/stem-like) CRC subtype. In addition, we have developed a diagnostic tool allowing us to select such patients for targeted therapy. We hope to renew our collaborations with the OPL in 'proof-of-concept' clinical and organoid-based studies as (phospho-)proteomics-based evaluation of drug response will be an essential part of future trial design."

Prof. Jos Jonkers, NKI, collaborator since 2007:

"The focus of our group is on the genetic dissection of human breast cancer through the use of advanced mouse models. In the past 9 years, our collaboration with the OPL has given us insight into the proteome of our genetically engineered mouse model for BRCA1- and BRCA2- associated hereditary breast cancer. The results of this fruitful collaboration have been published in 2 papers in the nr 1 proteomics paper in the field, Molecular and Cellular Proteomics and a joint KWF project. Currently we are using phosphoproteomics on our patient-derived xenograft models for homologous recombination repair deficient breast cancer. First pilot results have been very promising and I look forward to the results of this continuing joint discovery."

Prof. Jacco van Rheenen, NKI, collaborator since 2015:

"Our lab is a world-leader in the high resolution in vivo imaging of the behavior of cells in living mice. Last year, using in vivo imaging, we have shown how malignant tumor cells can phenocopy their behavior to more benign cells through extracellular vesicles (Zomer et al, Cell 2015). In collaboration with the OPL we are now tackling the molecular mechanisms behind this phenomenon. Together with the OPL, we are now identifying the protein content that is responsible for the metastatic behavior that is phenocopied. This may lead to the identification of new drug targets for tumor growth and metastasis.
We prepared our own samples at the OPL and we received excellent help with hands-on lab work and protocols optimized by the OPL. With the experience in data analysis of the OPL, we are sure we can get the best out of our data."

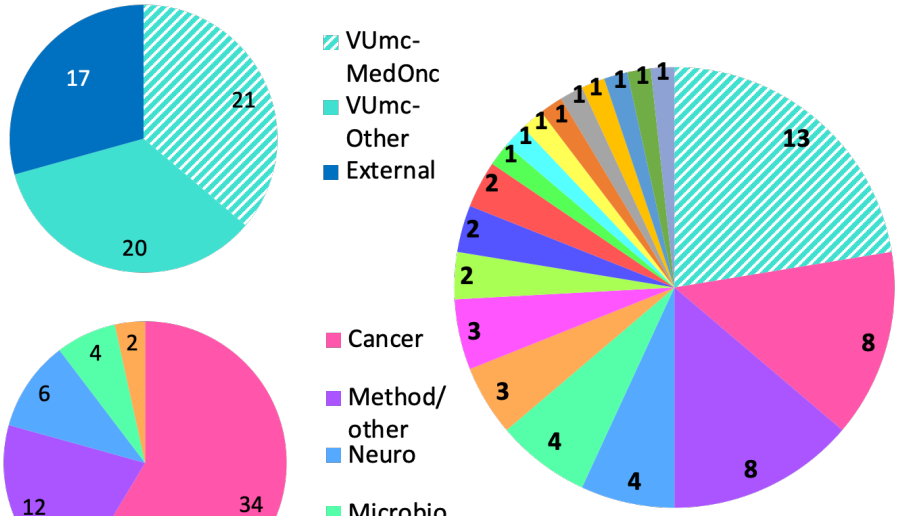
Quotes from the NL proteomics veld:

Prof. Rainer Bischoff (head of the Analytical Biochemistry Group at RUG and main participant in the Biomarker Development Center): “Digitalizing cancer proteomes will help to assess the individuality and heterogeneity of cancers in view of personalized cancer treatment’’.

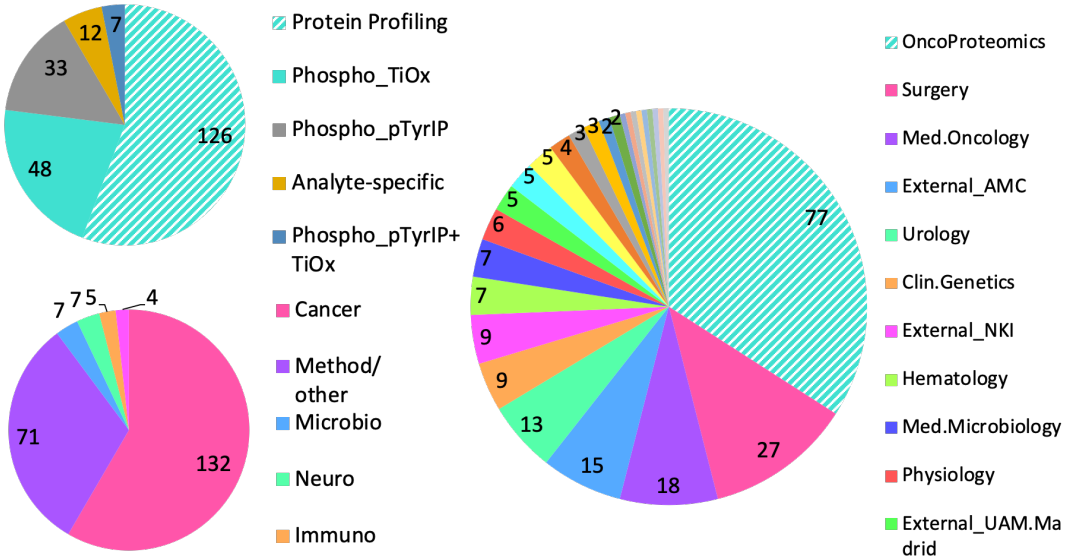
Dr. Arzu Umar (assistant professor and breast cancer proteome expert at EMC): “Dr. Jimenez is the founding mother of the proteomics community in the Netherlands with an enormous network in the proteomics field, both national and international, she is an expert in cancer proteomics, and has always been at the forefront of new developments and initiatives with the aim of translating state-of-the-art technologies and findings towards the clinic”.

Appendix OncoProteomics Laboratory Facts and Figures

Publications OncoProteomics Laboratory Last 5 years (2015-2020, n=58)



Mass Spectrometry Runs OncoProteomics Laboratory Last 5 years (2015-2020, n=226 exps)



Turn-around time between sample submission and data return :