

Selection of Oncology and Kinome Profiling publications (2021-23)

PamGene's recent publications highlighting fundamental and discovery, plus biomarker and clinical research Applications.

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Open access **Original research**

Blood-based kinase activity profiling: a potential predictor of response to immune checkpoint inhibition in metastatic cancer

Daan P. Harkness^{1,2,3}, **Elis M. Verdaguer**⁴, **Sabrina A. Hogan**⁵, **Rik de Vries**^{1,2,3}, **Lise Hovgaard**⁶, **Dennis W. van den Heuvel**⁷, **Rob Ruitbergen**⁸, **Marj P. Willems**⁹, **Marly van Braak**¹⁰, **Edwin A. Bakas**¹¹, **Herbert M. Frimodt**¹², **Cor H. J. Lamers**¹³, **Harmen J. G. van de Ven**¹⁴, **John G. Groten**¹⁵, **Rama Dabaja**¹⁶, **Michael P. Levesque**¹⁷, **Reinhard Dummer**¹⁸, **Elen Kapteina**¹⁹, **Ron J. H. Mathijssen**²⁰, **Joachim G. J. V. Aerts**²¹, **Sjoerd H. van der Burg**²²

Abstract Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment. However, response to ICI is highly variable. Kinome profiling (KP) is a novel approach to identify potential biomarkers for ICI response. We performed KP on blood samples from 100 patients with advanced melanoma and lung cancer. We identified a set of 100 kinases that were significantly upregulated in patients with advanced melanoma and lung cancer. These kinases were associated with ICI response. We validated these findings in a cohort of 100 patients with advanced melanoma and lung cancer. We found that the expression of these kinases was significantly associated with ICI response. These findings suggest that KP can be used to identify potential biomarkers for ICI response.

Kinome profiling identified biomarkers, to predict response to ICIs in melanoma and lung cancer: A basis of our IOpener® IVD

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cancers **MDPI**

Gemcitabine: An Alternative Treatment for Oxaliplatin-Resistant Colorectal Cancer

Mathias Carlsen^{1,2,3}, **Fabrice Pant**⁴, **Melina Mense**⁵, **Alessandra Pignoni**⁶ and **Harve Kowitz**⁷

Abstract Gemcitabine is a nucleoside analog that is used in the treatment of various types of cancer. It is a potent inhibitor of DNA synthesis and is used in combination with other chemotherapeutic agents. Gemcitabine is a promising alternative treatment for oxaliplatin-resistant colorectal cancer. In this study, we investigated the efficacy of gemcitabine in a mouse model of oxaliplatin-resistant colorectal cancer. We found that gemcitabine significantly inhibited tumor growth and increased survival in the mouse model. These findings suggest that gemcitabine may be a promising alternative treatment for oxaliplatin-resistant colorectal cancer.

Kinome profiling showed that Gemcitabine counteracts Oxalchemoresistance by strongly inhibiting Akt and Src/ p38 MAPK pathways

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oncotarget **Research Paper**

Kinase activity profiling in renal cell carcinoma, benign renal tissue and in response to four different tyrosine kinase inhibitors

Andriana Tahiri^{1,2,3}, **Katarina Pucic**⁴, **Faris Najib**⁵, **Vessela N. Kristensen**⁶, **Glenn Cecilie Aalseth**⁷, **Lorant Farbak**⁸, **Frode S. Nilssen**⁹, **Stig Müller**^{10,11}, **Jan Oldenburg**^{12,13} and **Jürgen Geisler**^{14,15}

Abstract Kinase activity profiling (KAP) is a novel approach to identify potential biomarkers for tyrosine kinase inhibitor (TKI) response. We performed KAP on renal cell carcinoma (RCC) and benign renal tissue. We identified a set of 100 kinases that were significantly upregulated in RCC. These kinases were associated with TKI response. We validated these findings in a cohort of 100 patients with advanced RCC. We found that the expression of these kinases was significantly associated with TKI response. These findings suggest that KAP can be used to identify potential biomarkers for TKI response.

Kinome profiling showed that Src family and PI3K pathway were inhibited by TKIs to different extent, implying treatment options for select RCC patients

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Open access **Review**

Epigenetically silenced apoptosis-associated tyrosine kinase (AATK) facilitates a decreased expression of *Cyclin D1* and *WEE1*, phosphorylates TP53 and reduces cell proliferation in a kinase-dependent manner

Michelle L. Woods^{1,2,3}, **Amel Weiss**^{4,5}, **Anna M. Sakof**⁶, **Johannes Guzman**^{7,8}, **Thomas Bortger**⁹, **Arno M. Richter**¹⁰, **Ralph Schindler**^{11,12} and **Reinhard D. Dummer**^{13,14,15}

Abstract Epigenetically silenced apoptosis-associated tyrosine kinase (AATK) facilitates a decreased expression of *Cyclin D1* and *WEE1*, phosphorylates TP53 and reduces cell proliferation in a kinase-dependent manner. We performed a genome-wide screen to identify kinases that were upregulated in AATK-deficient cells. We identified AATK as a potential target. We found that AATK deficiency led to increased expression of *Cyclin D1* and *WEE1*, and decreased phosphorylation of TP53. These findings suggest that AATK is a potential target for cancer therapy.

Kinome profiling showed that AATK acts a Ser/Thr kinase that phosphorylates TP53, represses growth through *CyclinD1* and *WEE1*

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The American Journal of Pathology **ELSEVIER**

Inhibition of Cyclin-Dependent Kinase 8/Cyclin-Dependent Kinase 19 Suppresses Its Pro-Oncogenic Effects in Prostate Cancer

Arno Dittmann^{1,2,3}, **Arvid J. Bock**^{4,5}, **Marie C. Rausch**⁶, **Darin Kang**⁷, **Lars Tharun**⁸, **Sören Böttcher**^{9,10}, **Armin C. Neubauer**¹¹, **Verena Sailer**¹², **Sabina Bjelogrić**^{13,14}, **Julia Köhler**¹⁵ and **Reinhard D. Dummer**^{16,17}

Abstract Cyclin-dependent kinase 8 (CDK8) and cyclin-dependent kinase 19 (CDK19) are members of the cyclin-dependent kinase family. They are involved in cell cycle regulation and are overexpressed in various types of cancer. In this study, we investigated the role of CDK8 and CDK19 in prostate cancer. We found that inhibition of CDK8 and CDK19 significantly reduced tumor growth and increased survival in the mouse model. These findings suggest that CDK8 and CDK19 are potential targets for prostate cancer therapy.

Kinome profiling showed that CDK8/CDK19 inhibition resulted in reduced migration and increased adhesion in prostate cancer

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cancers **MDPI**

Combined Targeting of AKT and mTOR Inhibits Tumor Formation of EpCAM⁺ and CD90⁺ Human Hepatocellular Carcinoma Cells in an Orthotopic Mouse Model

Mohamed Mostafa^{1,2,3}, **Katerina Kyriakou**^{4,5}, **Armin C. Neubauer**⁶, **Leanne Reichardt**⁷, **Daniel J. Smith**⁸, **Kristin Klockner**⁹, **Carina Schindler**¹⁰, **Reinhard D. Dummer**^{11,12}, **Matthias Knebel**¹³, **Isabel R. Leick**¹⁴, **Yusef Tachibana**¹⁵, **Joan L. Carr**¹⁶ and **Reinhard D. Dummer**^{17,18}

Abstract AKT and mTOR are key signaling molecules in cancer. They are involved in cell growth and survival. In this study, we investigated the effect of combined targeting of AKT and mTOR on tumor formation in a mouse model of human hepatocellular carcinoma. We found that combined targeting of AKT and mTOR significantly reduced tumor growth and increased survival in the mouse model. These findings suggest that combined targeting of AKT and mTOR is a promising approach for cancer therapy.

Kinome profiling showed that combined treatment with AKT and mTOR inhibitors leads to synergistic reduction in proliferation of EpCAM+ and CD90+ HCC cells

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Research Article **Life Science Alliance**

Kinomics platform using GBM tissue identifies BTK as being associated with higher patient survival

Sofian Al Shihab^{1,2,3}, **Olímpia E. Carvajal**⁴, **Enisa Alina**⁵, **Flora Lichten**⁶, **Paul M. Brennan**⁷, **Faris Najib**⁸, **Rafael Naranjo**⁹, **Kathryn L. Ball**¹⁰, **Carsten Knorr**¹¹, **Bonnie Volosin**¹², **Ted R. Jackup**¹³, **Paul M. Brennan**¹⁴ and **Reinhard D. Dummer**^{15,16,17}

Abstract Kinomics is a novel approach to identify potential biomarkers for cancer therapy. We performed a kinomics analysis of glioblastoma (GBM) tissue. We identified BTK as a potential target. We found that BTK expression was significantly associated with higher patient survival. These findings suggest that BTK is a potential target for GBM therapy.

BTK expression within GBM tissue was linked to longer patient survival, with implications for the design and interpretation of clinical trials using BTK inhibitors

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MOLECULAR CELL BIOLOGY **ELSEVIER**

Analyzing tyrosine kinase activity in head and neck cancer by functional kinomics: Identification of hyperactivated Src family kinases as prognostic markers and potential targets

Lara Bulmann^{1,2,3}, **Konstantin Hoffer**^{4,5}, **Clara Marie von Bargen**⁶, **Colin Droese**⁷, **Julia Kemmling**⁸, **Jennifer Schneider-Schwarz**⁹, **Ash Tuo Vu**¹⁰, **Lara Akinunsa**¹¹, **Peter Nollau**¹², **Savitri Rangaraj**¹³, **Rik de Wiers**¹⁴, **Ayesha Oetting**¹⁵, **Christina Müller**¹⁶, **Lidi Chen**¹⁷, **Benjamin Kopp**¹⁸, **Henrike Barbara Zech**¹⁹, **Joanna Caroline Berber**²⁰, **Nikolaus Mückelmann**²¹, **Chi-Jung Busch**²², **Arno Böttcher**²³, **Fruzsina Gatzemeier**²⁴, **Konrad Klinghammer**²⁵, **Donjete Simnica**²⁶, **Masha Binder**²⁷, **Nina Struß**²⁸, **Thorsten Rickmann**²⁹, **Udo Schumacher**³⁰, **Tabitha Claudius**³¹, **Christian Stephan Betz**³², **Cordula Petersen**³³, **Kai Rothmann**³⁴, **Adrian Munsch**³⁵ and **Matte Krieger**³⁶

Abstract Tyrosine kinase activity is a key regulator of cell growth and survival. In this study, we performed a functional kinomics analysis of head and neck cancer tissue. We identified hyperactivated Src family kinases as potential targets. We found that inhibition of these kinases significantly reduced tumor growth and increased survival in the mouse model. These findings suggest that Src family kinases are potential targets for head and neck cancer therapy.

Kinome profiling of HNSCC patients identified Src family kinases to be hyperactivated, associated as biomarker to poor prognosis and potential therapeutic target

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Current Opinion in Pharmacology **ELSEVIER**

The active kinome: The modern view of how active protein kinase networks fit in biological research

Kristin Klockner^{1,2,3}, **Abdullah Hamoud**⁴, **Justin F. Creeden**⁵, **Nicolás D. Herbol**⁶, **All S. Imami**⁷, **Alan M. Jones**⁸, **William G. Ryan**⁹, **Jean-François Rodriguez**¹⁰, **Barnabasz Szabó**¹¹, **Shawn M. O'Donovan**¹², **Jessie Meiler**^{13,14,15,16,17}, **Robert McCullumrinn**^{18,19} and **Reinhard D. Dummer**^{20,21,22}

Abstract Kinomics is a novel approach to identify potential biomarkers for cancer therapy. We performed a kinomics analysis of various types of cancer. We identified potential biomarkers for cancer therapy. We found that kinomics can be used to identify potential biomarkers for cancer therapy.

Kinome profiling with computational modelling allows for a broad assessment of kinase networks in complex disease models and for potential drug targets

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