SOMATO PUBLICATIONS

Current Trends in Medicine

International "PAK" Symposium at NYC (October 12, 2019)

Pathogenic Roles of PAK1 Including Oncogenesis and Ageing

Hiroshi Maruta[1]* and Edward Manser[2]

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ABSTRACT

PAK is the major "Pathogenic" Kinase (oncogenic/ageing enzyme) which is responsible for a wide variety of diseases/disorders such as cancers and AD (Alzheimer's disease), and eventually shortens our healthy lifespan.

This year marks the 25th anniversary of discovery of "mammalian" PAK, and eventually a few potent PAK-blockers such as Minnelide (prodrug of Triptolide), 15K (Ketorolac ester) and Mart-10 (Vitamin D_3 analog) have been developed for therapy of these PAK-dependent diseases (without any side effect), and promoting the longevity as well.

Celebrating this special occasion, we organized the first international PAK symposium at New York on October 12, 2019. The major aims of this historic symposium are: (i) sharing cutting-edge advance in PAK research and (ii) promoting the research collaboration among all of us (PAK experts) for further potentiation of clinically useful anti-PAK therapeutics. The symposium was held at Hotel Marriott "East Side", 525 Lexington Avenue, New York City, supported by PAK Research Foundation (Melbourne).

Symposium Program

Opening remark: Dr. Hiroshi Maruta

Session 1: 9:05-10:35

9:05-9:35 "Keynote Speech" by Dr. Edward Manser, IMCB, Singapore

Title: The Ups and Downs of PAK Signaling

9:35-10:05 by Dr. Jonathan Chernoff, Fox Chase Cancer Center, Philadelphia

Title: p21-activated Kinases (PAKs) as Therapeutic Targets in Cancer

10:05-10:35 by Dr. Gunda Georg, University of Minnesota

Title: Minnelide, A Prodrug of PAK1-blocking Triptolide, for Cancer Treatment

Break (10:35-10:50)

Session 2: 10:50-11:50

10:50-11:20 by Dr. Hiroshi Maruta, PAK Research Center, Melbourne

Title: PAK1-blockers for Cancer Therapy and Promotion of Longevity

11:20-11:50 by Dr. Laurie Hudson, University of New Mexico,

Title: R-ketorolac Blocks the Oncogenic RAC/CDC42-PAK1 Pathway

Lunch break: Noon-13:30

Afternoon sessions chaired by Dr. Ed Manser

Session 3: 13:30-15:00

13:30-14:00 by Dr. Thomas Adrian, MBR University, Dubai,

Title: Anti-cancer Property of PAK1-blockers, Frondoside A (FRA) and 15K

14:00-14:30 by Dr. Hong He, University of Melbourne Austin Hospital, Melbourne

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Title: Suppression of PAK1-dependent PD-L1 Expression for Better Cancer Therapy

14:30-15:00 by Dr. Maria Diakonova, University of Toledo, USA

Title: Tyr-phosphorylation of PAK1 by JAK and ETK for Breast Cancer Progression

Break (15:00-15:15)

Session 4: 15:15-16:15

15:15-15:45 by Dr. Jonathan Chernoff(on behalf of Dr. Wade Clapp)

Title: PAK1 Inhibition Reduces Tumor Size and Extends the Lifespan of NF2-null Mice

15:45-16:15 by Dr. Audrey Minden, Rutgers, the State Universityof New Jersey

Title: PAK4-blockers Down-regulate TORC2in Triple-Negative Breast Cancer Cells.

Closing remark: Dr. Ed Manser and a group photo session (figure x).

figure x: Speakers of PAK symposium (October 12, 2019):
From left to right: Drs. Minden, He, Manser (back), Maruta, Husdon (back), Georg, Diakonova (back), Adrian, Field (back) with his lap top used for "Sky" presentation by Dr. Chernoff. This photo was provided by Victoria Yang He.

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Current Trends in Medicine

International "PAK" Symposium at NYC (October 12, 2019)

The Ups and Downs of PAK Signaling

Edward Manser*

Institute of Molecular and Cell Biology, Singapore

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Introduction

The kinase ACK and p21-activated kinases (PAKs) were among the first effectors of Rho family GTPases (Rho/RAC/CDC42) to be discovered around1994.The ability of PAK1 to be directly activated *in vitro* by Rac1 and Cdc42 led to the notion that such protein kinases may be common downstream targets of Rho family. Among many Rho-associated kinases so far identified, PAKs seem to be the most evolutionarily ancient class.

In the search of downstream PAK1 substrates we discovered the PIX (RAC exchange factor) and its partner GIT, which in fact act 'upstream' of the kinase. In several contexts these protein scaffolds have been shown to be required for the function of PAK1-3 (RAC/CDC42-activated PAKs), as demonstrated in invertebrate models. We are interested in how PAKs regulate focal adhesion dynamics of mammalian cells. In order to understand the basis for PAK function in cells, we have used a variety of PAK inhibitors to investigate the immediate effects (10-45 min) of these drugs on the actin cytoskeleton. Under these conditions the activity of PAK1/PAK2 was demonstrated to promote turnover of acto-myosin pools and focal adhesions. I will discuss progress that has been made in uncovering the PAK phosphorylation targets that impinge on the cytoskeleton.

Biography

PhD (in Biophysics) from National Institute for Medical Research, London in 1986

1986-1987: Post doc, at Institute of Neurology, London. 1987 -1991: Research Fellow, Institute of Molecular and Cell Biology (IMCB), Singapore. 1995 -1999: Senior Scientist, Glaxo-IMCB Group. 2000-2008: Principal Investigator, GSK-IMCB group. 2008-2012: Senior PI, Institute for Medical Biology (IMB). 2008-2010: Deputy Director, Astar-NRP (Neuroscience Research Program) 2009-2012: Senior PI, Astar-NRP (Neuroscience Research Program) Currently, Senior PI, Institute of Molecular & Cell Biology (IMCB).

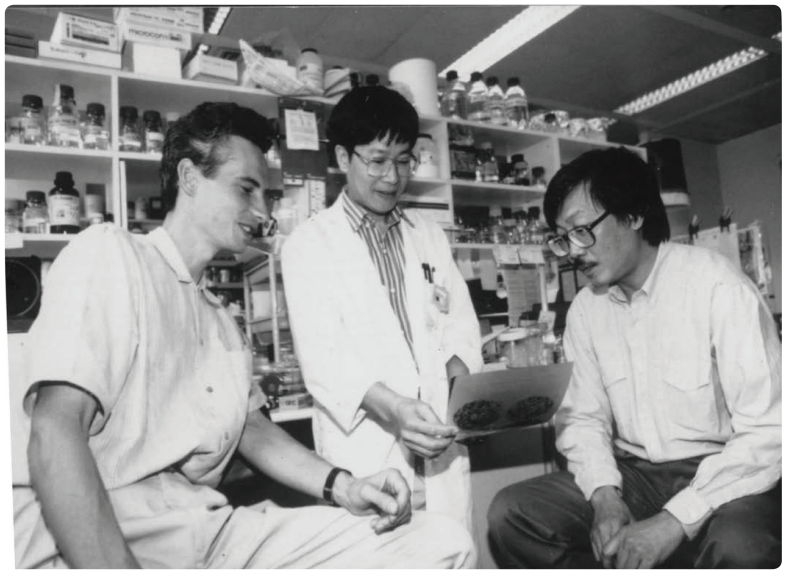

Figure 1: Ed Manser's team cloning the first mammalian PAK genes.

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Current Trends in Medicine

International "PAK" Symposium at NYC (October 12, 2019)

p21-activated Kinases (PAKs) as Therapeutic Targets in Cancer

Jonathan Chernoff*

Fox Chase Cancer Center, Philadelphia, USA

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ABSTRACT

Several lab groups have contributed to the discovery of p21 (RAC/CDC42)-activated kinases (PAKs) and to the elucidation of their cellular functions. Of the two PAK families, Group A PAKs (PAK1, -2, and -3) are the best studied, but this situation is gradually changing, and models of the signaling properties of both group A and group B PAKs have emerged. These models have been inferred primarily via the identification of PAK substrates, including those that are involved in the activation of the ERK, AKT, Aurora, and β-catenin pathways. In this presentation, I will discuss the roles of Group A and B PAKs in three cancer models and discuss the potential use of PAK-based small molecule and peptide inhibitors as therapeutic agents in cancer.

Biography

PhD and M.D. (in Biochemisty) from Mount Sinai School of Medicine, New York, in 1984

Resident, at University Health Center of Pittsburgh (1984-1987), Clinical Fellow at Beth Israel Hospital, Boston (1988-1990) and Postdoc at Harvard Uni (1988-1991). Joining the Fox Chase Cancer Center (FCCC), Philadelphia in 1991. Currently, Professor, Chief Scientific Officer and Deputy Director, Stanley P. Reimann Chair in Oncology Research (FCCC).

Figure 2: Jon Chernoff's team at FCCC.
Dr. Chernoff is a gentleman in white shirts around the middle.

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Current Trends in Medicine

International "PAK" Symposium at NYC (October 12, 2019)

Minnelide, a Prodrug of PAK1-blocking Triptolide, for Cancer Treatment

Gunda Georg*

Department of Medicinal Chemistry, University of Minnesota, USA

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ABSTRACT

Pancreatic cancer is the fourth leading cause of cancer related deaths in the United States, with a 5-year survival rate of around 10%. Despite significant research in the treatment of pancreatic cancer, the survival rate of patients with the disease has not significantly improved over the past few decades, mainly because 90% of pancreatic cancers are resistant to conventional chemotherapeutics (chemos, DNA poisons) such as gemcitabine. The low survival rate of patients with pancreatic cancer points towards a need for entirely different therapeutic strategies. Interestingly, the major reason for chemo-resistance is abnormal activation of the major oncogenic kinase PAK1. In fact natural PAK1-blockers such as propolis cure effectively even terminal pancreatic cancers. However, many of these PAK1-blockers are water-insoluble, and therefore their bioavailability is rather poor. Minnelide is a water-soluble phosphorylated form of a water-insoluble natural PAK1-blocker called Triptolide, and currently investigated in Phase I and Phase II clinical trials for the treatment of pancreatic, other gastrointestinal cancers and AML. The discovery of Minnelide and its preclinical development will be discussed.

Biography

PhD (in Medicinal Chemistry) from Philipps University Marburg, Germany in 1980

Postdoctoral, at Philipps University Marburg (1981) and University of Ottawa, Canada (1982). Currently Professor and Head at Department of Medicinal Chemistry at University of Minnesota, USA, and Director of Institute for Therapeutics Discovery and Development (ITDD).

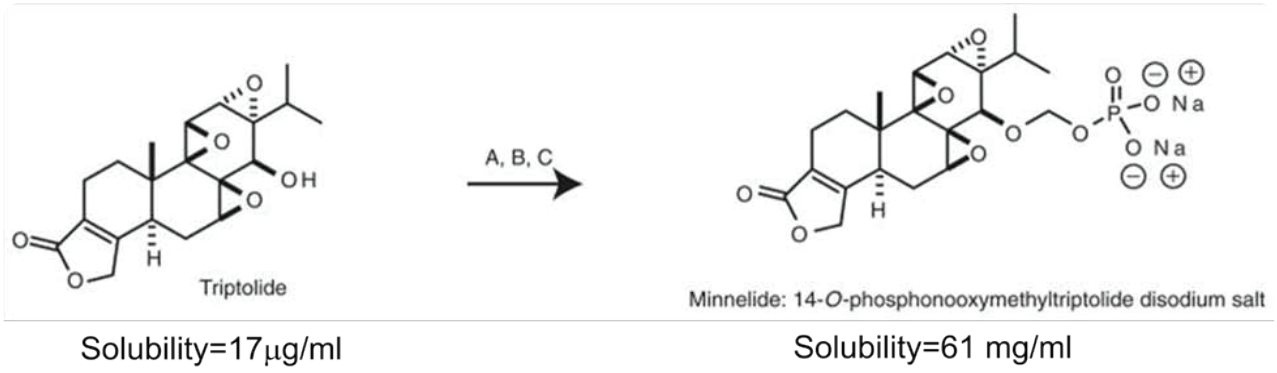

Figure 3: Synthesis of "Minnelide" from Triptolide.
Ref: R. Chugh, V.Sangwan, SP Patil, V. et al. A preclinical evaluation of Minnelide as a therapeutic agent pancreatic cancer. Sci Tensl Med.; 4(156): 156ra139 (2012).

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SOMATO PUBLICATIONS

Current Trends in Medicine

International "PAK" Symposium at NYC (October 12, 2019)

PAK1-blockers for Cancer Therapy and Promotion of Longevity

Hiroshi Maruta*

PAK Research Center, Melbourne, Australia

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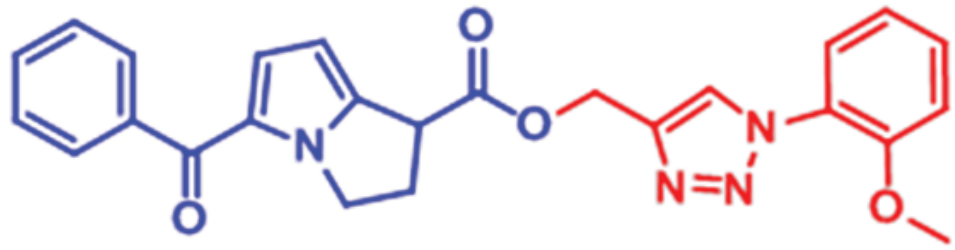
ABSTRACT

Back in 1994, 17 years after we discovered in amoeba the first member of PAK family (RAC/CDC42-activated kinases) that activates myosin I ATPase by heavy chain phosphorylation, the first "mammalian" PAKs were cloned by Ed Manser's team in Singapore. Among the 6 mammalian PAKs, PAK1 turned out to be the major "pathogenic" kinase responsible for a wide variety of diseases such as cancers, infectious/inflammatory diseases, AD (Alzheimer's disease), hypertension as well as ageing and melanogenesis. Thus, our team spent more than 2 decades to identify or develop a series of PAK1-blockers (natural or synthetic) for treatment of these diseases/disorders. Propolis (bee-product) is among the first natural PAK1-blockers that turned out to be useful for cancer therapy and promoting the longevity. However, PAK1-blocking ingredients in Propolis such as Artepillin C (ARC) and Caffeic Acid (CA) are COOH-bearing compounds whose cell-permeability is rather poor. Thus, we first managed to boost their cell-permeability 100-400 times by esterization with a water-soluble 1, 2, 3 triazolyl alcohol via Click Chemistry (CC). Eventually we could boost both anti-cancer and anti-PAK1 activity of an old COOH-bearing pain-killer (Ketorolac) via a similar CC approach by over 500 times. The resulting ester called "15K" extends the healthy lifespan of C. elegans by 30% at 10-100 nM, and suppresses both growth and metastasis of chemo-resistant human pancreatic cancer xenografts in mice with IC50 below 0.1 mg/kg/day with no side effect. Thus, we are intending to start its clinical trials ASAP.

Biography

PhD (in pharmaceutical sciences) from Tokyo University in 1972

NIH (1973-1980), Max-Planck-Institute in Munich (1980-1984), Yale and UCSD (1985-1987),Ludwig Institute for Cancer Research in Melbourne (1988-2006), PAK Research Center in Melbourne (2007-present).



(MW=442)

Figure 4: 1,2,3-Triazolyl Easter of Ketorolac (15K).
Ref: BC. Nguyen, H. Takahashi, Y. Uto, MD Shahinozzaman, S. Tawata, H. Maruta. 1,2,3-Triazolyl ester of Ketorolac: A "Click Chemistry"-based highly potent PAK1-blocking cancer-killer. Eur J Med Chem.; 126: 270-276 (2016).

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Current Trends in Medicine

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R-ketorolac Blocks the Oncogenic RAC/CDC42-PAK1 Pathway

Laurie G. Hudson

University of New Mexico, USA

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ABSTRACT

An old pain-killer called Ketorolac is a 1:1 racemic mixture of S- and R-forms. The S-form is the active component for its FDA indication in pain management that selectively inhibits cyclooxygenases such as COX-2. The biological function of R-form has remained unknown for decades, but recently recognized as a direct inhibitor of GTPases called Rac1 and Cdc42. Rac1 activity and expression are frequently elevated in tumors and a recent meta-analysis of 1,793 patients in 14 studies concluded that Rac1 expression was a poor prognostic indicator across cancers. Our analysis of the 298 Stage III and IV high-grade serous ovarian cancer (HGSOC) patients with outcomes data in The Cancer Genome Atlas (TCGA) demonstrates that high total RAC1 (but not CDC42) mRNA expression is associated with worse outcomes. R-ketorolac inhibits the serum /EGF-dependent Rac1 and Cdc42 activation, thereby inactivating their down-streams such as PAK1. R-ketorolac, but not S-ketorolac, inhibits Rac1-dependent cellular functions in cancer cell lines and primary ovarian tumor cells isolated from patient ascites fluids including inhibition of growth factor-stimulated formation of filopodia, cell adhesion to fibronectin and type I collagen, development of invadopodia, and tumor cell migration. *In vivo*, R-ketorolac decreases ovarian tumor cell implantation in the omentum, decreases tumor growth and increases survival of mice in a xenograft study using OVCAR8 ovarian cancer cells. These preclinical findings suggest that R-ketorolac may have beneficial actions in human ovarian cancer that could account for the reported improved patient outcomes associated with peri-operative ketorolac use. An initial clinical study of ovarian cancer patients was conducted following administration of racemic ketorolac for its FDA-approved indication in post-operative analgesia. Ketorolac was distributed to the peritoneum within 1 hour after IV administration, and at 6 hours, ketorolac levels in the peritoneal fluids were nearly equivalent to those present in the serum. At each of the time points (1, 6, and 24 h), peritoneal fluids were enriched in R-ketorolac compared to the S-form. R-ketorolac achieved concentrations in the peritoneal fluids at or above the IC_{50} (μM levels) for Rac1 and Cdc42 and resulted in time-dependent inhibition of Rac1 and Cdc42 in cells retrieved from the peritoneal compartment. R-ketorolac predominates in the peritoneal fluids and the S-form is virtually undetectable at 24 hours, indicating that the R-form is bioactive and accounts for the observed inhibition of the GTPases *in vivo*. We propose that the COOH-bearing Ketorolac and its highly cell-permeable analogs such as 15K (1,2,3-triazolyl ester) are potential therapeutics for a wide variety of cancers.

Biography

Ph. D. (Pharmacology/Toxicology) from Harvard University in 1985

Postdoc at UCSD (1985-1990). Assistant Prof at Northwestern University School of Medicine (1990-1997). Asssociate Prof. at UNM Health Sciences Ctr (1997-2003). Professor at Pharmaceutical Sciences, College of Pharmacy, UNM Health Sciences Ctr (2003-present).

Figure 5: Another group photo at PAK Symposium. Dr. Hudson is in front, 3rd from the left. The photo was taken by Dr. Maruta

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Current Trends in Medicine

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Anti-cancer Property of PAK1-blockers, Frondoside A (FRA) and 15K

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ABSTRACT

Among our anti-cancer marine compounds the most potent is a PAK1-inhibiting sulfated saponin called frondoside A (FRA) from a sea cucumber, *Cucumaria frondosa*. FRA inhibits the growth of multiple cancer cell lines, including pancreas and lungs with IC_{50} ranging 0.5–1 μM, similar to the IC_{50} against PAK-1. FRA inhibits tumor cell migration, invasion, growth *in vivo*, development of metastases and angiogenesis with IC_{50} below 1 mg/kg/day. Additionally, at low concentrations FRA acts as an immune-stimulant of cell-based immunity without significant effect on humoral immunity and blocks multidrug resistance by inhibiting P-glycoprotein activity. FRA has no effect on body weight, hematological parameters or on hepatic/renal function.

The anti-cancer effects of a more potentPAK1-blocker called 15K (highly cell-permeable ester of Ketorolac) were also tested. 15K inhibited the growth of several pancreatic cancer cell lines with IC_{50} ranging 41-88 nM *in vitro*. The effect of 15K was further investigated in an orthotopic xenograft model with gemcitabine-resistant human pancreatic cancer cell lines (AsPC-1 and BxPC-3) expressing luciferase in athymic mice. By the 28th day, 15K suppressed total burden (growth) of both AsPC-1 and BxPC-3 tumors (measured as radians/sec) with IC_{50} below 0.1mg/kg/day, i.p. 15K also reduced their metastasis in a similar manner. However, 15K had no effect on body weight or hematological parameters even at daily dose 5 mg/kg.

Biography

PhD (Biochem/Physiol) Royal Postgraduate Medical School (Imperial College), London in 1980

RPMS, London (1980-1985); Yale (1985-1988); Prof. and Director of Cancer Research, Creighton, Omaha (1988-2001); Prof. and Director of GI Cancer Research, Northwestern, Chicago (2001-2006); Prof and Chair UAEU (2006-2018); Prof and Chair of Research and Grad Studies, MBRU, Dubai, (2018-present).

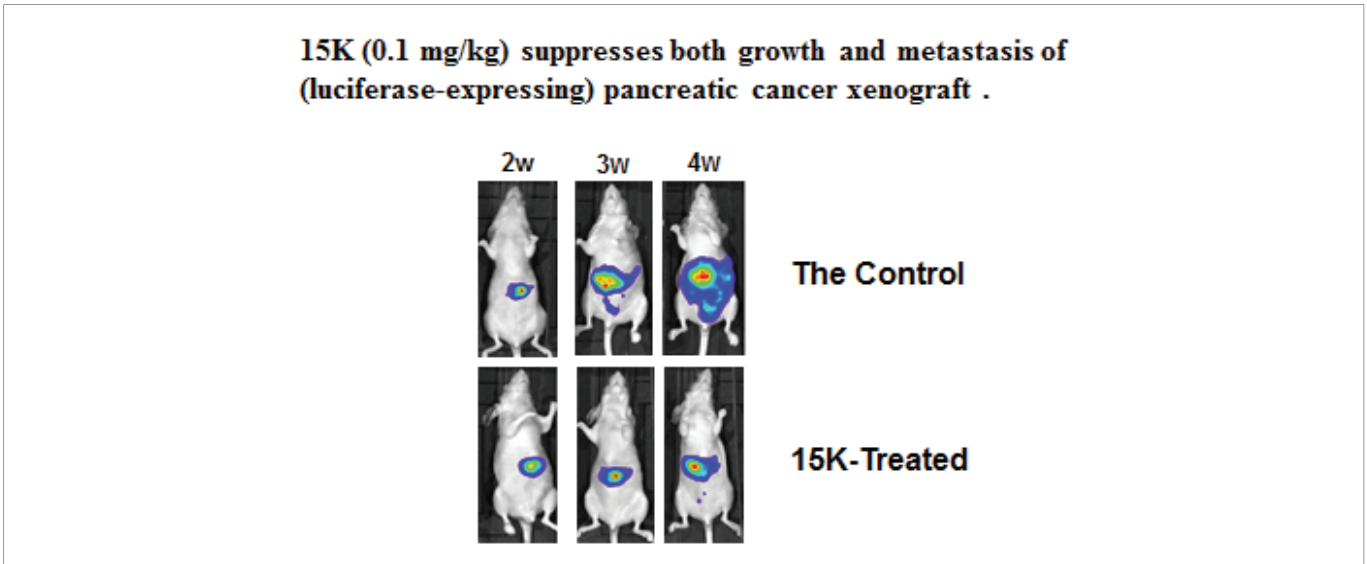

Figure 6: Ref: R. Hennig, A. Albawardi, S. Almarzooqi, et al. 1,2,3-Triazolyl Ester of Ketorolac (15K), a Potent PAK1-Blocker, Inhibits Both Growth and Metastasis of Human Pancreatic Cancer Orthotopic Xenografts in Mice. Drug Discov.Ther.; 13: 248-255 (2019).

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Current Trends in Medicine

International "PAK" Symposium at NYC (October 12, 2019)

Suppression of PAK1-dependent PD-L1 Expression for Better Cancer Therapy

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ABSTRACT

Immunotherapies have not yielded significant clinical benefits for pancreatic ductal adenocarcinoma (PDA) because of the existence of an immunosuppressive tumor microenvironment (TME) characterised by a desmoplastic stroma containing infiltrated immune cells and activated pancreatic stellate cells (PSCs). Inhibition of PAK1 (RAC/CDC42-activated kinase 1) suppressed the growth of PDA and PSCs, and up-regulated the tumor immune response. The aim of this study was to investigate the involvement of PAK1 in anti-tumor immunity. PAK1 expression, PSC activation, and intra-tumoral T cells, were analysed in murine and human PDA samples by immunohistochemistry and FACS. The correlation of PAK1 to PSC activation, intra-tumoral T cells and survival was calculated. The mechanism by which PAK1 affected anti-tumor immunity was investigated by measuring cancer cell survival after co-culturing with activated lymphocytes. In PDA patients low PAK1 expression, low activation of PSC and high $CD8^+$ T cell/PAK1 ratios correlated with longer overall survival. In a murine PDA model PAK1 knockout increased intra-tumoral $CD4^+$ and $CD8^+$ T cells, inhibited PSCs activation and extended survival. Inhibition of PAK1 reduced PSC-stimulated PDA cell proliferation, blocked PSC-mediated protection of PDA cells from killing by cytotoxic lymphocytes and decreased basal and PSC-stimulated PD-L1 expression in PDA cells, which further sensitized PDA cells to cytotoxic lymphocytes. Inhibition of PAK1 stimulates anti-tumor immunity by increasing intra-tumoral $CD4^+$ and $CD8^+$ T cells, and by sensitizing PDA cells to killing by cytotoxic lymphocytes via down-regulation of intrinsic and PSC-stimulated PD-L1 expression. Thus, inexpensivePAK1-blocking chemicals could replace the so-called immune check-point therapeutics (monoclonals) for the improved treatment of PDA.

Biography

M.D from Beijing Medical University (China) in 1987, and Ph.D. (in Molecular Biology) from University of Melbourne in 1994. Joining Ludwig Institute for Cancer Research (Melbourne Branch) as a postdoc in 1994. Joining the Department of Surgery of University of Melbourne (within Austin Health) in 2003, and currently a Senior Research Scientist at the above. Her major expertise is in roles of PAKs in cancers and immune system.

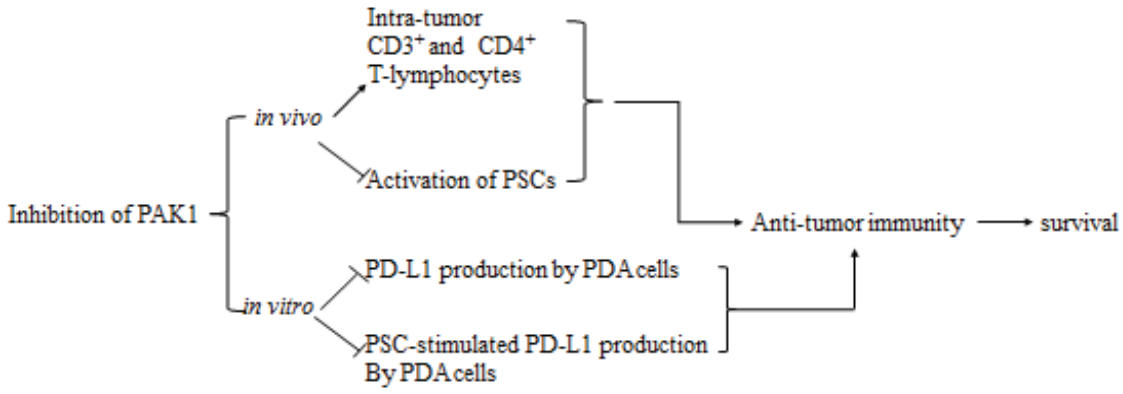

Figure 7: PAK1-blockers: stimulate anti-cancer immunity, thereby suppressing the cancer growth.
Ref. Wang K, Zhan Y, Huynh N, et al. Inhibition of PAK1 suppresses pancreatic cancer by stimulation of anti-tumour immunity through down-regulation of PD-L1. Cancer Lett. 2020; 472: 8-18.

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Current Trends in Medicine

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Tyr-phosphorylation of PAK1 by JAK and ETK for Breast Cancer Progression

Maria Diakonova*

University of Toledo, OH, USA

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ABSTRACT

In 2007, we demonstrated that PAK1 is a substrate of the Tyr-kinase JAK2 which is activated by hormone/cytokine prolactin (PRL). JAK2 phosphorylates PAK1 atTyr 153, 201 and 285 *in vivo* and *in vitro*. We identified Tyr285 as a site of PRL-dependent phosphorylation of PAK1 by JAK2. This phosphorylation enhances both PAK1 kinase activity and its ability to form protein/protein interactions (scaffolding properties of PAK1). We found that pTyr-PAK1 facilitates PRL-dependent motility of breast cancer cells via at least two mechanisms: (1) formation of paxillin/GIT1/ βPIX /pTyr-PAK1 complexes resulting in increased adhesion turnover, and phosphorylation of actin-binding protein filamin A. Increased adhesion turnover is the basis for cell migration and phosphorylated filamin A stimulates the kinase activity of PAK1 to facilitate cell motility. (2) pTyr-PAK1 also stimulates invasion of breast cancer cells in response to PRL and 3D-collagen IV by stimulating both transcription and secretion of MMP-1 and MMP-3 in a MAPK-dependent manner. We indeed confirmed that that pTyr-PAK1 enhances breast tumor growth and metastasis in a xenograft mouse model. Overall, our data illustrate the complex interaction between prolactin and the cell microenvironment in breast cancer cells and suggest a pivotal role for\ prolactin/pTyr-PAK1 signaling in breast cancer metastasis.

Although PRL and estrogen exert independent effect on breast cancer cells, there is cross-talk between them leading to synergetic breast cancer progression. We recently found that pTyr-PAK1is a common node for estrogen- and PRL-dependent pathways. An Estrogen-activated Tyr-kinase ETK directly phosphorylates PAK1 on Tyr153. Furthermore Estrogen-activated PKA phosphorylates Ser305 on estrogen receptor (ERα), while PRL-activated pTyr-PAK1 phosphorylates the same site of ERα, implying that maximal ERα phosphorylation is achieved when cells are exposed to both PRL and estrogen. However, anti-estrogen therapy by Tamoxifen (TAM) targets only the estrogen component. Notably, ERα phosphorylation at Ser 305 was implicated in TAM-resistance. Thus, a combination of JAK2-inhibitor and ETK-inhibitor that eventually blocks PAK1 would be a better approach for breast cancer therapy.

Biography

PhD (Cell Biology) from the Institute of Cytology Russian Academy of Science (St.-Petersburg, Russia) in 1993

Postdoc at the EMBL (Heidelberg, Germany) and the University of Michigan (Ann Arbor, MI, USA) (1995-2002). Research Assistant Professor at the University of Michigan (2002-2006). Assistant, Associate and Professor at the University of Toledo, OH (2006-present).

Figure 8: Maria Diakonova's team at Toledo Uni.

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Current Trends in Medicine

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PAK1 Inhibition Reduces Tumor size and Extends the Lifespan of NF2-null Mice

Wade Clapp*

Indiana University School of Medicine, Indianapolis, USA

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(Presented by Dr. Jonathan Chernoff on behalf of Dr. Clapp)

ABSTRACT

Neurofibromatosis Type II (NF2) is an autosomal dominant cancer predisposition syndrome in which germline haplo-insufficiency at the NF2 gene confers a greatly increased propensity for tumor development arising from tissues of neural crest derived origin. NF2 encodes the tumor suppressor, Merlin, and its biochemical function is incompletely understood. One well established function of Merlin is as a negative regulator of the kinase PAK1. In these studies we explore the role of PAK1 in Merlin deficient Schwann cells. We demonstrate that not only PAK1 and but also PAK2 are hyper-activated in Merlin deficient murine schwannoma and that genetic ablation of PAK1 alone, but not PAK2, ameliorates tumor formation in a genetically engineered mouse model (GEMM) of NF2. Moreover, germline genetic deletion of PAK1 was well tolerated while conditional deletion of PAK2 in Schwann cells resulted in significant morbidity and mortality. These data support the further development of PAK1 specific inhibitors and the therapeutic targeting of PAK1 in vestibular schwannoma and argue that PAK1 and PAK2 play clearly distinct (non-redundant) roles in Schwann cells.

Biography

M.D. from Indiana University School of Medicine in 1982

Postdoc training (1982-1991) at Indiana University (School of Medicine) and Case Western Reserve University. Joining Indiana University School of Medicine in 1991. Currently Professor (and Director of Tumor Microenvironment Program, IU Simon Cancer Center) at Indiana University (School of Medicine).

Figure 9: Wade Clapp's team at Indiana Uni. Dr. Clapp is in the back row, 5th from the left.

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Current Trends in Medicine

International "PAK" Symposium at NYC (October 12, 2019)

PAK4-blockers Down-regulate TORC2 in Triple-Negative Breast Cancer Cells

Audrey Minden*

Department of Chemical Biology, Rutgers, the State University of New Jersey, USA

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ABSTRACT

Triple negative breast cancer (TNBC) is difficult to treat due to lack of druggable targets. The kinase PAK4 is often highly expressed in TNBC cells. We previously found that inhibition of PAK4 with either siRNA or theanti-PAK4 drug KPT-9274 suppresses the growth of TNBC cells. In order to understand better how blocking PAK4 inhibits TNBC cell growth, we carried out RNA sequencing of TNBC cells treated with KPT-9274. As a result, we identified Rictor as a key target that is suppressed in the KPT-9274 treated cells. Rictor is a component of TORC2, a complex formed with the oncogenic Ser/Thr kinase TOR (target of rapamycin). TOR is important for controlling cell growth and metabolism, while PAK4 is associated with cell growth, survival, and migration. Our results suggest a new mechanism by which PAK4 inhibition may block the growth of cancer cells, by down-regulating TORC2 signaling.

Biography

PhD (in Genetics) from University of Illinois at Chicago, College of Medicine in 1992

Post doc at Dept. of Pharmacology, UCSD (1992-1996). Joining Columbia University, New York in 1996. Associate Professor: Dept. of Biological Sciences, Columbia University (2001-2006). Associate Professor at Susan Lehman Cullman Laboratory for Cancer Research, Dept. of Chemical Biology. Rutgers, the State University of New Jersey (2006-present).

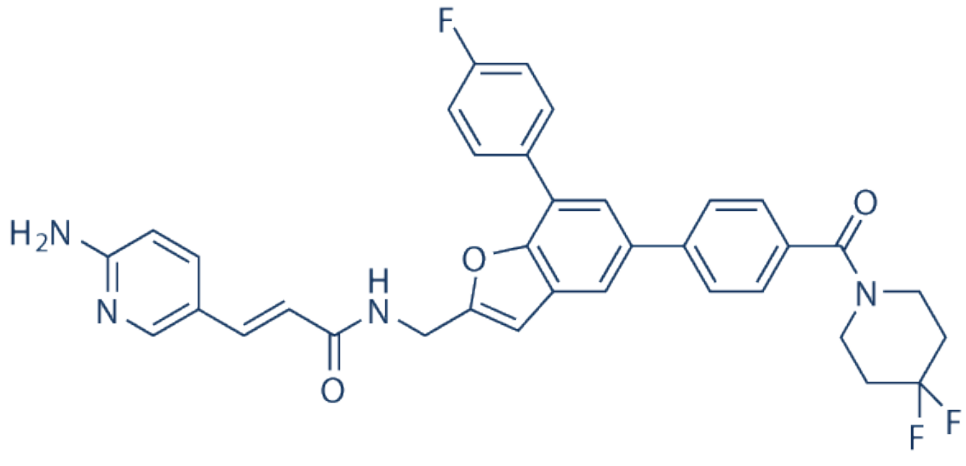

Figure 10: Chemical structure of KPT-9274.
Ref: Cordover E, Wei J, Patel C, et al. KPT-9274, an inhibitor of PAK4 and NAMPT, leads to down regulation of mTORC2 in triple negative breast cancer cells. Chem Res Toxicol. 2019 Dec 26.

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