

# Opening Lecture

## **Applying protein tyrosine phosphatase inhibitors in cancer therapeutics**

Author(s)

**Michel L. Tremblay**

Authors affiliation(s)

**Goodman Cancer Research Centre and Dept. of Biochemistry,  
McGill University, Montreal, Canada**



Abstract

The protein tyrosine phosphatase (PTP) gene family encodes for 107 genes in the human genome. This remarkable diversity is reflected in the function of these enzymes in important regulatory axes ranging from growth factor and cytokine signaling, to cell-cell interaction, cytoskeletal regulation and cell specification. Not surprisingly, the past 30 years of PTP studies have led to the identification of broad numbers of disease contexts where members of this family were found to be either mutated or inappropriately expressed, including cancer, metabolic, neurological and immune diseases.

Their diverse functions have also provided exciting opportunities to employ modulators of these enzymes to treat several diseases. Unfortunately, they remain largely impervious to targeting in clinical applications due to similarity of the catalytic domain, presence of charged residues, poor inhibitor uptake and other issues.

In this presentation, I will review several approaches that we have undertaken to target specific PTP enzymes in disease. Among those that I will discuss are our efforts to comprehend the roles and additive effects of two small intracellular PTPs, PTP1B and TC-PTP, and the therapeutic relevance of targeting these in prostate and pancreatic cancers, particularly through our new immunotherapy platform.

A second major interest of the laboratory has been to examine the oncogenic mechanisms of the trio of PTP4A enzymes, with a focus on our recent finding of their modulatory activity on the CNNM magnesium sensors. This represents a novel paradigm in cellular metabolism that places the PTP4A/CNNM protein complexes at the center of oncometabolism, infectious disease, and normal mammalian physiology.

Our overarching conclusion on PTP function is that protein tyrosine phosphatases act as finely tuned sensors of signaling output. Their stoichiometry is key to maintaining homeostasis. Therefore, their study and targeting must reflect this dosage effect since such functions are often poorly exposed in gene knock-out disease models, yet they are likely to open novel approaches in translational applications.

# Special Seminar

## Cancer heterogeneity and plasticity based on cancer stem cell biology

Author(s)

---

Hideyuki Saya



Authors affiliation(s)

---

Division of Gene Regulation, Institute for Advanced Medical Research,  
Keio University School of Medicine, Tokyo, Japan

Abstract

---

For several types of cancer, it is considered that a select subpopulation with stem-cell like properties gives rise to all other cells in the tumor mass. Cancer stem cells (CSCs) are therefore, by definition, a major contributor to tumor heterogeneity. However, CSCs themselves can display both intra- and intertumoral diversity and undergo phenotypic reprogramming in response to environmental cues.

The present study explores the metabolic characteristics of brain tumor stem cells, with a specific focus on their adaptation to nutrient and oxygen availability. We present our findings from an induced cancer stem cell model of glioma, based on orthotopic implantation of murine *Ink4a/Arf* <sup>-/-</sup> neural stem cells overexpressing HRasV12 into the brains of syngeneic mice. Our results show that brain tumors can contain stem cells with different metabolic characteristics and that this diversity can help survival in conditions of nutrient limitation. Moreover, in a subgroup of tumor stem cells, hypoxia can induce a reversible change of the main metabolic pathway.

In addition, we have recently found that differentiation property is a critical factor for tumorigenic activity of cancer stem cells. Based on our findings, we attempted to establish the transdifferentiation approach for treatment of cancer stem cells by using mouse osteosarcoma stem cell model.

# Invited Speaker 1

## **Protein phosphatase PP1-NIPP1 limits the DNA-repair capacity**

Author(s)

---

**Mathieu Bollen**

Authors affiliation(s)

---

**Laboratory of Biosignaling & Therapeutics,  
University of Leuven, Leuven, Belgium**



Abstract

---

PP1 is a member of the PPP superfamily of protein Ser/Thr phosphatases. It is a ubiquitously expressed enzyme that catalyzes over half of all protein dephosphorylation events in eukaryotic cells. In mammals PP1 interacts with over 200 PP1-interacting proteins (PIPs) that determine when and where the phosphatase acts. One of these PIPs is NIPP1, for nuclear inhibitor of PP1. To study the *in vivo* function of NIPP1 we have generated NIPP1 knockout models. A total NIPP1 knockout in mice is early embryonic lethal. However, the conditional knockout of NIPP1 in liver epithelial cells or skin keratinocytes has no major spontaneous phenotype, except for a moderate expansion of the stem-cell compartment. Strikingly, such NIPP1-deprived cells display a strongly enhanced DNA-repair capacity and a nearly complete resistance to mutagen-induced carcinogenesis. Conversely, the expression of a PP1-NIPP1 fusion in HeLa cells causes replication stress, as illustrated by the appearance of slow and stalled replication forks, and the accumulation of double-strand DNA breaks. Importantly, replication stress was not observed after the expression of PP1-NIPP1 fusions with mutated substrate-binding or PP1-anchoring domains of NIPP1. This strongly suggests that replication stress induced by PP1-NIPP1 stems from the dephosphorylation of FHA ligands by associated PP1. We are currently identifying the relevant substrates. Thus, our data indicate that PP1-NIPP1 limits the DNA-repair capacity.

## Invited Speaker 2

### Control of Lymphocytes by Protein Phosphatase-6 and SAPS1

David L. Brautigan

Authors affiliation(s)

Center for Cell Signaling, Department of Microbiology,  
Immunology & Cancer Biology. University of Virginia,  
Charlottesville, VA, USA



Abstract

Protein phosphatase-6 (PP6) is one member of the PPP protein Ser/Thr phosphatase family, conserved as an essential gene among eukaryotes starting with Sit4 in yeast. PP6 is distinct from its closest PPP relatives PP2A and PP4, because of specific association with conserved regulatory subunits called SAPS (*Sit4-Associated Proteins*). SAPS1 and PP6 participate in signaling that links TNF $\alpha$  to NF- $\kappa$ B and enhance the stability of I $\kappa$ -B $\epsilon$ . We discovered by proteomics that SAPS1 associates with one of three ANKRD (Ankyrin-repeat domain) subunits to form trimeric PP6 holoenzymes. SAPS1 also co-immunoprecipitates with DNA-PK (DNA-dependent protein kinase) and is required for DNA-PK activation in response to irradiation. We have produced SAPS1 deficient mice that display accelerated lethality in response to whole body irradiation.

We examined lymphocyte development in these *SAPS1*<sup>-/-</sup> mice. There were no differences in T or B cells in the primary lymphoid organs or in the mature B or T cells in the spleen or blood of SAPS1 deficient mice compared to control mice, however there was an increase in eosinophils. Eosinophilia is often associated with type 2 immune responses and we discovered a huge increase in serum IgE in SAPS1 deficient mice, as well as an increase in CD4 T cells producing IL-4. Our hypothesis is that SAPS1/PP6 constrains CD4 T-helper 2 (Th2) cells from inappropriate Th2 differentiation. More recent results examined SAPS1/PP6-dependent changes in intracellular signaling of CD4<sup>+</sup> T cells from SAPS1 deficient mice, based on changes in gene expression and proteomics.

## Identifying the human calcineurin signaling network

Author (s)

**Martha S Cyert<sup>1</sup>, Callie Wigington<sup>1</sup>, Jagoree Roy<sup>1</sup>,  
Nikhil Damle<sup>1</sup>, Huy Ngyuen<sup>2</sup>, Kurt Thorn<sup>2</sup>, Polly Fordyce<sup>3</sup>,  
Ylva Ivarsson<sup>4</sup>, and Norman Davey<sup>5</sup>**



Authors affiliation(s)

<sup>1</sup>Department of Biology, Stanford University, Stanford, CA, USA

<sup>2</sup>Department of Biochemistry and Biophysics, UCSF, San Francisco, CA, USA <sup>3</sup>Departments of Bioengineering and Genetics,

Stanford University, Stanford, CA, USA <sup>4</sup>Department of Chemistry - BMC, Uppsala University, Sweden <sup>5</sup>Conway Institute of Biomolecular and Biomedical Sciences, University College Dublin, Ireland

Abstract

Systems-level analyses of phosphorylation-based signaling networks has transformed our understanding of kinase function, but knowledge of phosphatase signaling has lagged behind, primarily because global approaches to identify phosphatase substrates are lacking. Calcineurin, the conserved Ca<sup>2+</sup>/calmodulin-dependent protein phosphatase and target of immunosuppressants, FK506 and Cyclosporin A, is ubiquitously expressed, and critically regulates Ca<sup>2+</sup>-dependent processes in the immune system, heart, and brain. However, in the literature only ~30 human substrates are currently attributed to calcineurin.

We are using novel experimental and computational approaches to identify human proteins that contain “PxIxIT” and “LxVP” sequences. Calcineurin specifically recognizes its targets by binding to these short linear motifs (SLiMs), which occur preferentially in intrinsically disordered domains, and are challenging to identify due to sequence degeneracy and low affinity for calcineurin. Proteome peptide Phage Display (ProP-PD) was used to identify calcineurin-binding sequences of the PxIxIT and LxVP types experimentally from predicted disordered regions of the human proteome. These sequences directly identify novel and known calcineurin targets, and provide a large set of calcineurin-binding peptides for robust computational prediction of novel PxIxIT and LxVP-containing proteins in the human proteome. We also characterized the amino acid preference at each position of the PxIxIT and LxVP motifs using a novel technology that employs microfluidically-produced, spectrally-encoded beads, on which peptides are synthesized. Beads containing 96 distinct peptides, each with a unique spectral code, were incubated with calcineurin in a single volume and imaged to determine the amount of calcineurin that binds to each peptide.

Novel calcineurin-binding sequences that are identified either experimentally or computationally are validated using a high throughput calcineurin-binding assay, and their parent proteins tested for interaction with calcineurin in HEK-293 cells. These studies are identifying many new candidate substrates for calcineurin that include ion channels, kinases, transcription factors and receptors, and reveal new points of cross-talk between calcineurin and other signaling pathways in human cells. Furthermore, these approaches can be broadly applied to systematic characterization of any SLiM-based signaling network.

## Epigenetic Regulation by Notch Signaling in Glioma

Author(s)

---

**Yutaka Kondo**

Authors affiliation(s)

---

**Dept. of Epigenomics, Nagoya City University**

**Graduate School of Medical Sciences, Nagoya, Japan**



Abstract

---

In the neural stem cell, the Notch signaling pathway plays a dominant role in inhibiting differentiation through the activities of its downstream effectors, such as Hairy and enhancer of split 1/5 (Hes1/5), which repress the implementation of neurogenic programs. In the context of glioma tumorigenesis, Notch signaling has been shown to promote glioma stem cell (GSC) self-renewal and to suppress GSC differentiation. However, the mechanism by which Notch signaling and its downstream effectors maintains the stemness properties of GSCs through the function of a certain set of genes, such as SOX2, MYC and Nestin, remains unresolved. Here, we found that a specific Notch-regulated long non-coding RNA, TUG1, the expression of which is regulated by the Notch signaling pathway, was highly expressed in GSCs. TUG1 coordinately promotes self-renewal by sponging miR-145 in the cytoplasm and recruiting polycomb to repress differentiation genes by locus-specific methylation of histone H3K27 via YY1 binding activity in the nucleus. Furthermore, we developed new antisense oligonucleotides targeting TUG1 coupled with a potent drug delivery system, which can be used intravenously to provide efficient and selective delivery to glioma cells at sufficient concentrations to acquire anti-tumor effects. Our observations indicate that Notch-directed TUG1 is an effective epigenetic modulator that regulates the cancer stem cell population.

## Invited Speaker 5

### **Structural basis for PTPN3-p38gamma complex involved in colon cancer progression**

Author(s)

**Kai-En Chen, Shu-Fang Hsu, Shu-Yu Lin, Meng-Ru Ho,  
Chia-Cheng Chou, Andrew H.-J. Wang and Tzu-Ching Meng**



Authors affiliation(s)

**Institute of Biological Chemistry,  
Academia Sinica and Institute of Biochemical Sciences,  
National Taiwan University, Taipei, Taiwan**

Abstract

The Ras signaling cascade acts as a key driver in human colon cancer progression. Among the modules in this pathway, p38gamma (MAPK12) and its specific phosphatase PTPN3 (PTPH1) are critical regulators responsible for Ras oncogenic activity. However, the molecular basis for their interaction is completely unknown. Here we report the unique architecture of the PTPN3-p38gamma complex by employing an advanced hybrid method integrating X-ray crystallography, small-angle X-ray scattering (SAXS) and chemical cross-linking/mass spectrometry (CX-MS). Our crystal structure of PTPN3 in complex with the p38gamma phosphopeptide presented a unique feature of the E-loop that defines the substrate specificity of PTPN3 towards fully activated p38gamma. The low-resolution structure demonstrated the formation of an active-state or a resting-state complex of PTPN3-p38gamma. We showed a regulatory function of PTPN3's PDZ domain, which stabilizes the active-state complex through interaction with the PDZ-binding motif of p38gamma. Using SAXS and CX-MS approaches, we found that binding of the PDZ domain to the PDZ-binding motif lifts the atypical auto-inhibitory constraint of PTPN3, enabling efficient tyrosine dephosphorylation of p38gamma to occur. Our findings emphasize the potential of structural approach for PTPN3-p38gamma complex that may deliver new therapeutic strategies against Ras-mediated oncogenesis in colon cancer.

# Invited Speaker 6

## A Surprising Role for PTP1B in Breast Cancer

Author(s)

---

**Benjamin G. Neel**

Authors affiliation(s)

---

**Perlmutter Cancer Center, NYU-Langone Medical Center,  
NY, NY.**



Abstract

---

Deletion of *Ptpn1*, which encodes Protein-Tyrosine Phosphatase-1B (PTP1B), delays the onset of *Her2/Neu*-driven breast cancers in mice, but the underlying mechanism(s) has been controversial. The role of PTP1B in *HER2*<sup>+</sup> human breast cancer also is unresolved. We found that, unexpectedly, PTP1B protects *HER2*<sup>+</sup> breast cancer (BC) cell lines and tumors from hypoxia-induced death. Although there was no consistent effect of *PTPN1* depletion or PTP1B inhibition on growth factor signaling or proliferation of *HER2*<sup>+</sup> BC cells *in vitro*, PTP1B-deficient *HER2*<sup>+</sup> xenografts showed increased hypoxia, necrosis and impaired growth. *PTPN1*-knockdown (1B-KD) also sensitized *HER2*<sup>+</sup> BC lines to hypoxia-induced death *in vitro*. Remarkably, all known hypoxia response pathways appear normal or increased in PTP1B-deficient cells. Instead, biochemical and genetic analysis reveal a novel pathway for regulating tumor cell response to hypoxia, and a new function for PTP1B, acting via the Moyamoya disease gene *RNF213*, in the control of  $\alpha$ -KG-dependent dioxygenases in *HER2*<sup>+</sup> BC cells. Control of  $\alpha$ -KG-dependent dioxygenase activity by this novel PTP1B/*RNF213* hypoxia-regulatory pathway appears to be critical for the survival of breast cancer and possibly other malignant cells in the tumor microenvironment.

# Invited Speaker 7

## Multiple Roles for eIF2 $\alpha$ Phosphatases in the Unfolded Stress Response

Author(s)

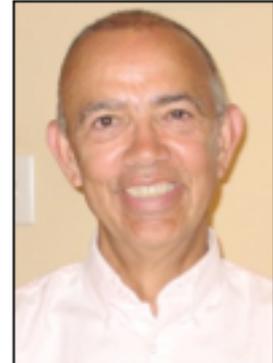
---

**Shirish Shenolikar**

Authors affiliation(s)

---

**Duke-NUS Medical School, Singapore and Duke University, USA**



Abstract

---

Transient repression of mRNA translation is a universal response of all eukaryotic cells to perturbations in their metabolic or growth environment. This “integrated stress response” temporarily slows general protein synthesis and allows cells to redirect their efforts towards translating mRNAs encoding stress response proteins that are required to overcome the “stress”. Failure to execute this complex translational and transcriptional response triggers cell death and likely contributes to a wide variety of chronic human diseases. The repression of global mRNA translation is mediated via the phosphorylation of a single serine-51 on the eukaryotic initiation factor, eIF2 $\alpha$ . Subsequently, the transcriptional and translational upregulation of GADD34 (Growth Arrest- and DNA Damage-induced transcript 34), a regulator of protein phosphatase-1 (PP1), assembles an eIF2 $\alpha$  phosphatase that restores general protein synthesis. Cells also express another eIF2 $\alpha$  phosphatase, containing the regulatory subunit, CReP (constitutive repressor of eIF2 $\alpha$  phosphorylation). This presentation will review our current understanding of the distinct roles of GADD34- and CReP-containing eIF2 $\alpha$  phosphatases in the control of transcriptome and translome in unstressed cells and in stressed cells experiencing the unfolded protein response. The data highlight some of the challenges and opportunities in therapeutic targeting of eIF2 $\alpha$  phosphatases with small molecules to treat diabetes, cancer and neurodegenerative disorders.

# Invited Speaker 8

## Roles of protein phosphatases in cell polarity control

Author(s)

---

**Takashi Toda**

Authors affiliation(s)

---

**Hiroshima Research Center for Healthy Aging (HiHA),  
Department of Molecular Biotechnology,  
Graduate School of Advanced Sciences of Matter,  
Hiroshima University, Hiroshima, Japan**



Abstract

---

A molecular understanding of how cells define their own morphology in a spatiotemporal manner is one of the fundamental issues in biology and medical science. Rod shaped fission yeast *Schizosaccharomyces pombe* cells are highly polarised; cells grow only from cell tips with constant width. Interestingly, during G2 phase of the cell cycle, cells undergo a drastic polarity transition from monopolar to bipolar growth. This regulatory point is referred to as NETO, New-End-Take-Off.

We have identified Calcineurin (PP2B), and Casein kinase 1 $\gamma$  (Cki3) as critical determinants of NETO timing. Upon activation of the DNA replication checkpoint, a condition to delay NETO, *cki3*- or calcineurin mutant cells commit NETO prematurely. Intriguingly, *cki3* cells exhibit premature NETO even under unperturbed conditions. By contrast, PP1 is required for the execution of NETO. Subsequent analyses indicate that the kelch-repeat containing polarity factor Tea1 and the microtubule-associated protein Tip1 (CLIP170) are downstream factors, whose phosphorylation and dephosphorylation play a decisive role in NETO timing. In this talk, I will present our recent results in growth polarity control in fission yeast and discuss the general significance of these findings.

Kume K, Koyano T, Kanai M, Toda T, Hirata D (2011) Calcineurin ensures a link between the DNA replication checkpoint and microtubule-dependent polarized growth. *Nat Cell Biol* 13: 234-242.

Koyano T, Konishi M, Martin SG, Ohya Y, Hirata D, Toda T, Kume K (2015) Casein kinase 1 $\gamma$  ensures monopolar growth polarity under incomplete DNA replication downstream of Cds1 and calcineurin in fission yeast. *Mol Cell Biol* 35: 1533-1542.

Koyano T, Barnouin K, Snijders AP, Kume K, Hirata D, Toda T (2015) Casein kinase 1 $\gamma$  acts as a molecular switch for cell polarization through phosphorylation of the polarity factor Tea1 in fission yeast. *Genes Cells* 20: 1046–1058.

## Drugging the undruggable: exploiting PTP1B as a therapeutic target

Author(s)

**Nicholas K. Tonks**

Authors affiliation(s)

**Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA**



Abstract

The protein tyrosine phosphatases (PTPs) are important regulators of signal transduction. These cysteine-dependent phosphatases hydrolyze phosphoester bonds in proteins and non-protein substrates. Overall, the objective of the lab is to characterize the structure, regulation and function of PTPs, to define their role in critical tyrosine phosphorylation-dependent signaling events under normal and pathophysiological conditions, and to identify novel therapeutic targets and strategies based upon the PTPs themselves, or from components of the signaling pathways they regulate.

PTP1B plays a well-established role in down-regulating insulin and leptin signaling and is a validated therapeutic target for diabetes and obesity. Furthermore, PTP1B is a positive regulator of signaling by the HER2 oncoprotein tyrosine kinase, such that inhibition of the phosphatase also abrogates breast tumorigenesis and metastasis. Several potent, specific, reversible small molecule inhibitors of PTP1B have been developed, but they target the conserved, highly charged active site and exhibit poor oral bioavailability, which limits their drug development potential. This led industry to dismiss the members of the PTP family as “undruggable”.

In contrast, I will illustrate how a detailed understanding of the structure, regulation and function of PTP1B, which has been generated in an academic setting, has revealed new approaches to the development of small molecule drug candidates that target this enzyme. For example, we are exploiting a physiological mechanism of regulation of PTP function by reversible oxidation and inactivation that is induced following stimulation of cells, such as with insulin or leptin. Our data illustrate that stabilization of the oxidized, inactive form of PTP1B with appropriate therapeutic molecules may offer a novel paradigm for phosphatase drug development. Furthermore, we have identified small molecule inhibitors that target a unique allosteric site in the regulatory, C-terminal segment of PTP1B. In addition to stimulating insulin signaling, we have demonstrated that such allosteric PTP1B inhibitors antagonize HER2 function, including abrogation of tumor metastasis in the NDL2 transgenic mouse model of HER2-positive breast cancer. This new approach to cancer therapy is currently the subject of a clinical trial. Finally, the application of such inhibitors is revealing new functions of PTP1B and suggesting new indications in which inhibition of PTP1B may be of therapeutic benefit, such as for treatment of the autism spectrum disorder Rett syndrome.

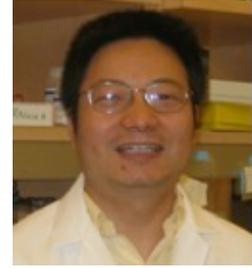
# Invited Speaker 10

## **PTPRT is a tumor suppressor that regulates intestinal stem cell proliferation**

Author(s)

---

**Zhenghe Wang**



Authors affiliation(s)

---

**Department of Genetics and Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH 44122, USA**

Abstract

---

Protein tyrosine phosphatase receptor-type T (PTPRT) is frequently mutated in a variety of human cancers including colon cancer. We demonstrated that PTPRT normally functions as a tumor suppressor using three different colon tumor models: (1) PTPRT knockout mice are highly susceptible to carcinogen azoxymethane-induced colon tumor; (2) PTPRT knockout increase incidence of AOM-DSS-induced colon tumors; and (3) PTPRT knockout increase the size of colon tumors in the *Apc<sup>min</sup>* mouse genetic background. Recently, intestinal stem cells marked by *Lgr5* are shown to be potential cell original of colon cancers. Interestingly, we found that *Lgr5*<sup>+</sup> intestinal stem cells in PTPRT knockout mice are more proliferative than in the wild-type (WT) mice. Using a phospho-proteomics approach, we identified and validated STAT3 as a direct substrate of PTPRT. Moreover, phospho-STAT3 is up-regulated in the intestinal crypts of PTPRT knockout mice compare to WT mice. These studies suggest that PTPRT-regulated STAT3 signaling pathway that plays important roles in intestinal homeostasis and colorectal tumorigenesis.

# Speaker 1

## The roles of PTPROt in chronic lymphocytic leukemia

### Author(s)

---

**Ari Elson<sup>1</sup>, Jean Wakim<sup>1</sup>, Esther Arman<sup>1</sup>,  
Shirly Becker-Herman<sup>2</sup>, Matthias P. Kramer<sup>2</sup>, and Idit Shachar<sup>2</sup>**

### Authors affiliation(s)

---

**Departments of Molecular Genetics<sup>1</sup> and Immunology<sup>2</sup>,  
The Weizmann Institute of Science, Rehovot 76100, Israel**



### Abstract

---

The hematopoietic tyrosine phosphatase PTPROt is a putative tumor suppressor in B cell chronic lymphocytic leukemia (CLL), where its expression is reduced. In order to examine the role of PTPROt in CLL we abrogated expression of PTPROt in mice and followed progression of CLL in them. Unexpectedly, complete loss of PTPROt delayed disease detection and progression and lengthened survival, indicating that PTPROt fulfills a novel tumor-promoting role in CLL. PTPROt-deficient tumor cells exhibited reduced B-cell receptor (BCR) signaling and increased apoptosis and autophagy. Inhibition of BCR/Src family kinases (SFK) in CLL cells induced apoptosis in a dose-dependent manner, indicating these events are linked causally. Complete loss of PTPROt thus reduces SFK activity, leading to reduced BCR signaling and reduced tumor cell survival, in agreement with the weakened CLL phenotype of PTPROt-deficient mice. These findings uncover non-redundant, cell-autonomous roles for PTPROt in support of BCR signaling and survival of CLL cells. In contrast, loss of only one Ptprot allele induced the opposite phenotype - earlier detection and progression of CLL and reduced mouse survival, consistent with the putative tumor suppressing role of PTPROt. Tumor cells from mice lacking one Ptprot allele exhibited normal BCR signaling and cell death, suggesting that their more aggressive disease is associated with its earlier initiation or dissemination. PTPROt thus functions in CLL as an obligate haploinsufficient tumor suppressor, a class of gene products whose expression levels determine their functions as tumor promoters or tumor suppressors. Partial loss of PTPROt generates the strongest disease phenotype, suggesting that its intermediate expression levels in CLL in humans are selected for.

## Speaker 2

### **Protein tyrosine phosphatase 1B deficiency in podocytes protects against hyperglycemia-induced renal injury**

Author(s)

**Yoshihiro Ito<sup>1</sup>, Ahmed Bettaieb<sup>1</sup>, MingFo Hsu<sup>1</sup>,  
Shinichiro Koike<sup>1</sup>, Aline Mello<sup>1</sup>, Fawaz G. Haj<sup>1</sup>**

Authors affiliation(s)

**University of California Davis<sup>1</sup>, CA, USA**



Abstract

Diabetic nephropathy is one of the most devastating complications of diabetes, and growing evidence implicates podocyte dysfunction in disease pathogenesis. Protein tyrosine phosphatase 1B (PTP1B; encoded by PTPN1) is an established metabolic regulator *in vivo* but its metabolic functions in podocytes remains unexplored. To that end, we generated podocyte-specific PTP1B knockout (pod-PTP1B KO) mice and determined alterations under normoglycemia and streptozotocin (STZ)- and high fat diet (HFD)-induced hyperglycemia. pod-PTP1B KO mice displayed significant improvement in renal function and glucose homeostasis under STZ- and HFD-induced hyperglycemia. Consistent with these findings, podocyte PTP1B deficiency was associated with increased renal insulin signaling and enhanced autophagy with corresponding decrease in inflammation and fibrosis. These effects were recapitulated in E11 murine kidney podocytes with lentiviral-mediated PTP1B knockdown, consistent with being cell-autonomous. Moreover, reconstitution of PTP1B in knockdown cells reversed the improved insulin signaling and autophagy demonstrating that they were likely a consequence of PTP1B deficiency. Together, these findings identify PTP1B in podocytes as a significant contributor to signaling events following hyperglycemia-induced damage, and suggest that PTP1B inhibition in podocytes may be of value in combating podocytopathies.