Pin1 Timeline

Year	Major advances with references
1996	Pin1 is identified in combined NIMA-suppressing and -interacting screens as the only PPIase essential for mitosis in yeast[1]
1997	Pin1 is the only PPIase specific to pSer/Thr-Pro motifs[2,3]
1999	Pin1 WW domain mediates its substrate recognition[4] Pin1 is depleted and cannot restore P-tau231 function in AD[5] Pin1-/- mice develop normally[6]
2000	Pin1-catalyzed *cis* to *trans* isomerization promotes P-tau231 dephosphorylation by *trans*-specific PP2A[7] CSF P-tau231 is a biomarker in AD[8]
2001-2002	Pin1 is overexpressed and promotes multiple oncogenic pathways in cancer[9-12]
2002	Pin1 regulates p53 function in genotoxic response[13-15]
2002-2003	Pin1 promotes germ cell proliferation[12,16]
2003	Pin1-/- mice are prone to age-dependent tau-related neurodegeneration[17]
2004	Pin1-/- mice are resistant to tumorigenesis by oncogenic Ras or Neu[18]
2005	Pin1 is activated in asthma and increases GM-CSF levels[19] Prospective evidence for the inverse relationship between AD and cancer[20]
2006	Pin1-catalyzed *cis* to *trans* isomerization of P-APP668 inhibits amyloidogenic processing and Ab secretion in AD[21]
2008-2010	Pin1 promotes HIV replication and integration[22,23]
2010	Pin1 regulates flowering signaling pathways[24]
2011	Pin1 promotes TLR signaling and immunity[25]
2012	Stereo-specific antibodies reveal that *trans* and *cis* P-tau231 are physiologic and early pathogenic in AD, respectively[26] Pin1 regulates neuron stem cells[26]
2013	Pin1 promotes signaling pathways in heart hypertrophy[27]
2013-2015	Pin1 promotes signaling pathways in diabetes[28,29]
2014	Pin1 drives normal and cancer stem cells[30,31]
2015	*Cis* P-tau231 underlies TBI/CTE and can be targeted by *cis* mAb[32] HTS uncovers Pin1 as a major target for ATRA in APL and breast cancer[33] Parasites secrete Pin1 to maintain host cell transformation[34]
2016	Pin1 is activated in lupus and promotes autoimmunity[35] Pin1 regulates PIN-FORMED protein 1 (PIN1) and root gravitropism[36]
2017	CSF *cis* P-tau231 and blood P-tau231 are an early diagnostic and prognostic biomarker in acute and chronic TBI[37,38]
2018	Pin1 is a major target for ATRA and ATO to synergistically block multiple cancer pathways and eliminate CSCs[39]
2019	Pin1 isomerization of BRCA1-BARD1 promotes replication fork protection[40] *Cis* P-tau231 antibody enters human clinical trials for safety and efficacy[41]
2020	Intratesticular Pin1 protein delivery rescues male infertility[42]
2021	Blood *cis* P-tau231 is probably the earliest biomarker in incipient AD[43] *Cis* P-tau231 underlies VCID and can be targeted by *cis* mAb[44] *Cis* P-tau231 is necessary and sufficient to cause and spread neurodegeneration resembling early AD and VCID[44] Pin1 regulates genome organization and function during stress[45] Sulfopin is the most potent and specific Pin1 inhibitor[46] Pin1 drives the desmoplastic and immunosuppressive TME[47] Pin1 inhibitors eradicate pancreatic cancer by synergizing with immunochemotherapy[47]

References

1 Lu, K. P., Hanes, S. D. & Hunter, T. A human peptidyl-prolyl isomerase essential for regulation of mitosis. *Nature* **380**, 544-547 (1996).

2 Yaffe, M. B. *et al*. Sequence-specific and phosphorylation-dependent proline isomerization: A potential mitotic regulatory mechanism. *Science* **278**, 1957-1960 (1997).

3 Ranganathan, R., Lu, K. P., Hunter, T. & Noel, J. P. Structural and functional analysis of the mitotic peptidyl-prolyl isomerase Pin1 suggests that substrate recognition is phosphorylation dependent. *Cell* **89**, 875-886 (1997).

4 Lu, P. J., Zhou, X. Z., Shen, M. & Lu, K. P. A function of WW domains as phosphoserine- or phosphothreonine-binding modules. *Science **283***, 1325-1328 (1999).

5 Lu, P. J., Wulf, G., Zhou, X. Z., Davies, P. & Lu, K. P. The prolyl isomerase Pin1 restores the function of Alzheimer-associated phosphorylated tau protein. *Nature* **399**, 784-788 (1999).

6 Fujimori, F., Takahashi, K., Uchida, C. & Uchida, T. Mice lacking Pin1 develop normally, but are defective in entering cell cycle from G(0) arrest. *Biochem Biophys Res Commun* **265**, 658-663 (1999).

7 Zhou, X. Z. *et al*. Pin1-dependent prolyl isomerization regulates dephosphorylation of Cdc25C and tau proteins. *Mol Cell* **6**, 873-883 (2000).

8 Kohnken, R. *et al*. Detection of tau phosphorylated at threonine 231 in cerebrospinal fluid of Alzheimer's disease patients. *Neurosci Lett* **287**, 187-190 (2000).

9 Wulf, G. M. *et al*. Pin1 is overexpressed in breast cancer and potentiates the transcriptional activity of phosphorylated c-Jun towards the cyclin D1 gene. *EMBO J*. **20**, 3459-3472 (2001).

10 Ryo, A., Nakamura, N., Wulf, G., Liou, Y. C. & Lu, K. P. Pin1 regulates turnover and subcellular localization of beta-catenin by inhibiting its interaction with APC. *Nature Cell Biol* **3**, 793-801 (2001).

11 Ryo, A. *et al*. Pin1 is an E2F target gene essential for the Neu/Ras-induced transformation of mammary epithelial cells. *Mol Cell Biol* **22**, 5281-5295 (2002).

12 Liou, Y. C. *et al*. Loss of Pin1 function in the mouse causes phenotypes resembling cyclin D1-null phenotypes. *Proc. Natl. Acad. Sci. USA* **99**, 1335-1340 (2002).

13 Wulf, G. M., Liou, Y. C., Ryo, A., Lee, S. W. & Lu, K. P. Role of Pin1 in the regulation of p53 stability and p21 transactivation, and cell cycle checkpoints in response to DNA damage. *J Biol Chem* **277**, 47976-47979 (2002).

14 Zacchi, P. *et al*. The prolyl isomerase Pin1 reveals a mechanism to control p53 functions after genotoxic insults. *Nature* **419**, 853-857 (2002).

15 Zheng, H. *et al*. The prolyl isomerase Pin1 is a regulator of p53 in genotoxic response. *Nature* **419**, 849-853 (2002).

16 Atchison, F. W., Capel, B. & Means, A. R. Pin1 regulates the timing of mammalian primordial germ cell proliferation. *Development* **130**, 3579-3586. (2003).

17 Liou, Y.-C. *et al*. Role of the prolyl isomerase Pin1 in protecting against age-dependent neurodegeneration. *Nature* **424**, 556-561 (2003).

18 Wulf, G., Garg, P., Liou, Y. C., Iglehart, D. & Lu, K. P. Modeling breast cancer in vivo and ex vivo reveals an essential role of Pin1 in tumorigenesis. *EMBO J*. **23**, 3397-3407 (2004).

19 Shen, Z. J., Esnault, S. & Malter, J. S. The peptidyl-prolyl isomerase Pin1 regulates the stability of granulocyte-macrophage colony-stimulating factor mRNA in activated eosinophils. *Nat Immunol* **6**, 1280-1287 (2005).

20 Roe, C. M., Behrens, M. I., Xiong, C., Miller, J. P. & Morris, J. C. Alzheimer disease and cancer. *Neurology* **64**, 895-898 (2005).

21 Pastorino, L. *et al*. The prolyl isomerase Pin1 regulates amyloid precursor protein processing and amyloid-beta production. *Nature* **440**, 528-534 (2006).

22 Watashi, K. *et al*. Human immunodeficiency virus type 1 replication and regulation of APOBEC3G by peptidyl prolyl isomerase Pin1. *J Virol* **82**, 9928-9936, doi:10.1128/JVI.01017-08 (2008).

23 Manganaro, L. *et al*. Concerted action of cellular JNK and Pin1 restricts HIV-1 genome integration to activated CD4+ T lymphocytes. *Nat Med* **16**, 329-333, doi:10.1038/nm.2102 (2010).

24 Wang, Y., Liu, C., Yang, D., Yu, H. & Liou, Y. C. Pin1At encoding a peptidyl-prolyl cis/trans isomerase regulates flowering time in Arabidopsis. *Mol Cell* **37**, 112-122, doi:S1097-2765(09)00924-1

25 Tun-Kyi, A. *et al*. Essential role for the prolyl isomerase Pin1 in Toll-like receptor signaling and type I interferon-mediated immunity. *Nature Immunol* **12**, 733-741 (2011).

26 Nakamura, K. *et al*. Prolyl isomerase Pin1 regulates neuronal differentiation via β-catenin. *Mol. Cell. Biol*. **32**, 2966-2978. (2012).

27 Toko, H. *et al*. Regulation of cardiac hypertrophic signaling by prolyl isomerase pin1. *Circulation research* **112**, 1244-1252, doi:10.1161/CIRCRESAHA.113.301084 (2013).

28 Lv, L. *et al*. Essential role of Pin1 via STAT3 signalling and mitochondria-dependent pathways in restenosis in type 2 diabetes. *J Cell Mol Med* **17**, 989-1005, doi:10.1111/jcmm.12082 (2013).
29 Paneni, F. *et al*. Targeting prolyl-isomerase Pin1 prevents mitochondrial oxidative stress and vascular dysfunction: insights in patients with diabetes. *Eur Heart J* **36**, 817-828, doi:10.1093/eurheartj/ehu179 (2015).
30 Luo, M. L. *et al*. Prolyl isomerase Pin1 acts downstream of miR200c to promote cancer stem-like cell traits in breast cancer. *Cancer Res* **74**, 3603-3616, doi:10.1158/0008-5472.CAN-13-2785 (2014).
31 Rustighi, A. *et al*. Prolyl-isomerase Pin1 controls normal and cancer stem cells of the breast. *EMBO molecular medicine* **6**, 99-119, doi:10.1002/emmm.201302909 (2014).
32 Kondo, A. *et al*. Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. *Nature* **523**, 431-436 (2015).
33 Wei, S. *et al*. Active Pin1 as a target of all-trans retinoic acid in acute promyelocytic leukemia and breast cancer. *Nature Med* **21**, 457-466 (2015).
34 Marsolier, J. *et al*. Theileria parasites secrete a prolyl isomerase to maintain host leukocyte transformation. *Nature* **520**, 378-382 (2015).
35 Wei, S. *et al*. Pin1-Targeted Therapy for Systemic Lupus Erythematosus. *Arthritis Rheumatol* **68**, 2503-2513, doi:10.1002/art.39741 (2016).
36 Xi, W., Gong, X., Yang, Q., Yu, H. & Liou, Y. C. Pin1At regulates PIN1 polar localization and root gravitropism. *Nature communications* **7**, 10430, doi:10.1038/ncomms10430 (2016).
37 Albayram, O. *et al*. Cis P-tau is induced in clinical and preclinical brain injury and contributes to post-injury sequelae. *Nature communications* **8**, 1000 (2017).
38 Rubenstein, R. *et al*. Comparing plasma phospho tau, total tau, and phospho tau–total tau ratio as acute and chronic traumatic brain injury biomarkers. *JAMA neurology* **74**, 1063-1072 (2017).
39 Kozono, S. *et al*. Arsenic targets Pin1 and cooperates with retinoic acid to inhibit cancer-driving pathways and tumor-initiating cells. *Nature communications* **9**, 3069 (2018).
40 Daza-Martin, M. *et al*. Isomerization of BRCA1-BARD1 promotes replication fork protection. *Nature* **571**, 521-527 (2019).
41 Safety and Tolerability of PNT001 in Healthy Adults https://clinicaltrials.gov/ct2/show/NCT04096287 (2019).
42 Kim, W. J. *et al*. Intratesticular Peptidyl Prolyl Isomerase 1 Protein Delivery Using Cationic Lipid-Coated Fibroin Nanoparticle Complexes Rescues Male Infertility in Mice. *ACS nano* **14**, 13217-13231 (2020).
43 Ashton, N. J. *et al*. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. *Acta Neuropathol* **141**, 709-724 (2021).
44 Qiu, C. *et al*. Cis P-tau underlies vascular contribution to cognitive impairment and dementia and can be effectively targeted by immunotherapy in mice. *Science Transl Med* **13**, eaaz7615 (2021).
45 Napoletano, F. *et al*. The prolyl-isomerase PIN1 is essential for nuclear Lamin-B structure and function and protects heterochromatin under mechanical stress. *Cell Rep* **36**, 109694 (2021).
46 Dubiella, C. *et al*. Sulfopin is a covalent inhibitor of Pin1 that blocks Myc-driven tumors in vivo. *Nat Chem Biol* **17**, 954-963 (2021).
47 Koikawa, K. *et al*. Targeting Pin1 renders pancreatic cancer eradicable by synergizing with immunochemotherapy. *Cell* **184**, 4753-4771 (2021).