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BIDMC Pin1 Portfolio: Full Suite of IP for Drug Target Pin1

➤ **Pin1-Related Therapeutics, Diagnostics, Compositions for Drug Researchers**

Consider all the protein phosphorylation events that regulate biology. If phosphorylation occurs on a serine or threonine next to a proline, Pin1 probably governs the biological significance of that phosphorylation by controlling the adjacent proline's *cis-trans* conformation. Discovered and pioneered by BIDMC's Dr. Kun Ping Lu since 1995, research on this target is now enjoying new momentum.

Pin1 is a peptidyl-prolyl isomerase catalyzing the *cis-trans* conversion of prolines adjacent to phosphoserine or phosphothreonine residues.

Pin1's medical significance is best understood for breast cancer where it regulates ErbB2, HER2, Raf and cyclin D1. Evidence is also abundant that Pin1 regulates prostate cancer biology. It will likely serve as a key drug target in a wide variety of other cancers, too, given that Pin1 is over-expressed in ~70% of all human cancers.

Pin1 plays a major role in cancer development. Though present and highly regulated in normal physiology, Pin1 activity correlates with disease and is known to have a major impact on cancer development in numerous and diverse research studies.

For example, in mice, Pin1 knockout suppresses oncogenesis induced by ablation of tumor suppressor p53 and prevents oncogenes such as Ras or HER2/Neu from inducing tumors. Conversely, in mice, Pin1 over-expression results in tumorigenesis. In humans, polymorphisms that inhibit Pin1 expression are associated with reduced risk for cancer. In parallel, many human tumors over-express Pin1 where its expression correlates with poor clinical outcome.

Pin1 is required for the activation of many oncogenes such as β -catenin, c-Jun, c-fos, NF- κ B, cyclin D1, Raf-1, RAR α , Stat3, c-Myb, HER2/Neu, and Notch, as well as viral oncoproteins Hbx1 and Tax. At the same time, Pin1 inactivates tumor suppressors including AIB1/SRC-3, p53, Mcl-1, FOXO, PML, C/EBP, SMRT, Smad, and Pin2/TRF1.

Importantly for drug researchers, Pin1 is a tractable drug target. It is readily assayable and research shows congruency in mechanism of action across a range of phenotypic assays including enzymology, *in vitro* cell culture, xenografts, and other *in situ* mouse cancer models. Notably, drug research for Pin1 is gaining promise with new technology recently developed by Dr. Lu— antibodies specific for the *cis* or *trans* conformers of Pin1 substrates.

Moreover, many high resolution Pin1 structures are known and high-affinity small molecule ligands and peptide inhibitors are available as research probes for the development of new Pin1 drugs. Indeed, these first generation ligands serve as drug leads for ongoing drug research.

Market: Oncology

Lead Indications: Breast, Prostate Cancer

- ✓ 519,000 breast cancer deaths (WW, '04)
- ✓ 186,000 prostate cancer cases (US, '08)

Commercialization:

- ✓ Rx, Dx, HTS and Composition claims
- ✓ Ready pairing with biomarkers
- ✓ Flexible licensing options

Competitive Advantages:

- ✓ Exclusive opportunities for a dominant IP position around a major target, including 11 issued patents

Stage of Development:

In vivo proof-of-concept in mice
 Ample human genetic data
 Drugability established

Patent / Licensing Status:

Available for exclusive licenses

Case Ref #	Filing #	Aspect
BIDMC 106	U.S. Patent #6,495,376	Method of inhibiting Pin1 with phosphopeptide, peptide mimetics
BIDMC 270	U.S. App. #12/218,838; CA Patent #2,392,917; EPO Patent #0098 2293.3	Pin1 immunohistochemistry or PCR-based diagnostic for diagnosing and staging cancers
BIDMC 278	U.S. Patent #6,462,173	Peptide, phosphopeptide, peptidomimetic inhibitors of Pin1 & methods of inhibiting Pin1 to treat cancer
BIDMC 974	Pending App. #11/632,588	Peptide inhibitors of Pin1 and uses thereof
BIDMC 986	Pending App. #11/623,672	Cyclic peptide inhibitors; case managed with Cornell; focus is on amyloid processing, but may inform cancer research
BIDMC 1061	Pending App. #61/255,341	Method and compositions for Pin1 screening & diagnostics; still unpublished assay methods make Pin1 drug development much more tractable
S98014	U.S. Patent #5972697	Pin1 nucleic acid sequence; relevance to diagnostics & biomarkers
S98014A	U.S. Patent #5952467	Pin1 sequence; e.g., purified human Pin1 protein
S98014B	U.S. Patent #6596848	Antibodies that bind to Pin1 & to select domains of Pin1; relevance to diagnostics & biomarkers
S98014C	U.S. Patent #7164012	Composition of matter for Pin1 nucleic acids & select domains of Pin1; relevance to diagnostics & biomarkers
S98014D	U.S. Patent #7125955	Composition of matter comprised of purified protein corresponding to select domains of Pin1 (WW, PPlase)
S98014E	U.S. Patent #7125677	Diagnostic applications relying on correlation between detection of Pin1 protein in cell & clinical care decision
S98014F	U.S. Patent #7148003	Screening methods that involve Pin1 protein

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