Supplementary Note

Supplementary Figure 1. Comparative pathology of breast tumors in NDL2-*ptpn1*$^{-/-}$ and NDL2-*ptpn1*$^{+/+}$ mice.

In addition to the analysis of tumor burden and multiplicity, we compared mammary whole mounts from MMTV-NDL2 mice containing either *PTP1B* wild-type or homozygous mutants (Supplementary Fig. 1). Careful examination of mammary gland whole mounts revealed that NDL2-*ptpn1*$^{+/+}$ animals exhibited a number of nodular masses amongst hyperplastic and dysplastic tissue at 0.3 week after palpable tumor, whereas NDL2-*ptpn1*$^{-/-}$ mice only presented hyperplastic lobuloalveloar endbuds (Supplementary Fig. 1B *vs* C). After 4 to 6 weeks of tumor initiation, both groups presented a severe altered branching, hyperplastic progression and neoplasia in the fat pad (Supplementary Fig. 1D-E *vs* A). However, all these features were less pronounced in the absence of *PTP1B* (Supplementary Fig. 1D-F *vs* E-G, respectively).

Supplementary Figure 2. Unaltered Src phosphorylation during mammary tumor progression in NDL2-*ptpn1* null mice

Since numerous tumors and cell lines overexpressing ErbB2 show high levels of activated Src 19 and because previous *in vitro* studies have identified PTP1B as a potent activator of Src by dephosphorylating its negative tyrosine regulatory site in human breast cancer cell lines 20, we examined the relative levels of Src activity and expression in breast tumor samples of our NDL2-*ptpn1* wild-type and null animals (Supplementary Fig. 2). Tumor lysates were subjected to western blot analysis using phosphospecific antibodies

against the inhibitory phosphorylation site of Src (Y529). To confirm this result, we also performed immunoblot using a phosphospecific antibody against the activating phosphorylation site of Src (Y418) and we observed a time-dependent decrease in Y418 phosphorylation resulting in decreased Src activity during tumor progression in both group of animals (data not shown).

Supplementary Figure 3. Administration of PTP1B inhibitor in NDL2-*ptpn1*$^{+/+}$ normalizes glucose levels

Glucose levels remains similar and lower than wild-type animals (5.71 ± 0.13 mmol.L-1; $P < 0.05$, data not shown) in both PTP1B inhibitor-administered NDL2-*ptpn1*$^{-/-}$ group (4.40 ± 0.09 mmol.L-1; $P < 0.05$) and vehicle-administered NDL2-*ptpn1*$^{-/-}$ group (4.35 ± 0.12 mmol.L-1; $P < 0.05$) all over the 21-days treatment and further in time. PTP1B inhibitor administration lowered glucose levels in the NDL2-*ptpn1*$^{+/+}$ group between day-6 of treatment up to 10 days after the end of treatment with an average of 4.50 ± 0.09 mmol.L-1 ($P < 0.05$) as compared to vehicle-administered NDL2-*ptpn1*$^{+/+}$ group (5.58 ± 0.17 mmol.L-1; $P < 0.05$)(Supplementary Fig. 3).

Supplementary Table1. Summary of phenotypic abnormalities in MMTV-PTP1B transgenic mice.

Four different female funders (A, B C and D from a second generation F2) were bred to FVB male to induce pregnancy in order to activate MMTV promoter and to synchronize tumor occurrence. Female were sacrificed after the weaning of the second, fifth or seventh pregnancy. Tissue mammary gland were processed according to routine procedures and

embedded in paraffin. Sections were cut and stained with H&E for histopathological diagnosis. A minimal diffuse mammary gland acinar hyperplasia was observed after 2 litters. However, after 5 or 7 litters mice developed mammary gland carcinoma papillary type. This tumor is well differentiated and composed of numerous finger-like projections supported by a fibrovascular stroma and covered by neoplastic epithelium. The rest of mammary gland was composed of hyperplastic acini, mild, with few mitoses and little atypia (nuclear pleomorphism). There was also focal squamous metaplasia in the mammary gland of one mouse analyzed. The rest of the mammary gland was composed of hyperplastic acini, minimal, with few mitoses and little atypia (nuclear pleomorphism). All these data provide unambiguous evidence that PTP1B transgene may drive tumors by its own.