**Supplementary Materials and Methods**

**RNA library preparation and sequencing**

Total RNA was extracted from vector- and PDE5-stable MCF-7 clones as described (Gu G et al., J Cell Phisiol 2012; 227:3363-72). RNA concentration was determined with NanoDrop-1000 spectrophotometer and quality assessed with Agilent-2100-Bioanalyzer and Agilent-RNA-6000 nanocartridges (Agilent Technologies). High quality RNA from three-independent purifications for each experimental point was used for library preparation. Indexed libraries were prepared from 1μg/ea. of purified RNA with TruSeq-RNA-Sample-Prep-Kit (Illumina) following suppliers. Libraries quality controls were performed using Agilent-2100-Bioanalyzer and Agilent DNA-1000 cartridges and concentrations were determined with Qubit-2.0 Fluorometer (Life Technologies). Libraries were sequenced (paired-end, 2×100 cycles) at a concentration of 8pmol/L per lane on HiSeq2500 platform (Illumina) as described (Dago DN, et al BMC Genomics 2015; 16:367). RNA sequencing data have been deposited in the EBI ArrayExpress database (http://www.ebi. ac.uk/arrayexpress) with Accession Number E-MTAB-3801.

**Classification of molecular subtypes**

In breast cancer, utilization of immunohistochemistry as a surrogate for molecular classification by gene expression profiling has been used in large population-based studies and has been shown to provide an acceptable level of accuracy for determining molecular phenotypes (Collins LC, et al. Breast Cancer Res Treat 2012;131:1061-6; Carey LA, et al. JAMA 2006;295:2492-502; Yang XR, et al. Cancer Epidemiol Biomarkers Prev 2007;16:439-43.). Using histologic tumor-grade obtained by central pathology review and biomarkers (estrogen and progesterone receptors (ER/PR) and HER2 status) extracted from pathology reports, cases were classified as one of four molecular subtypes. Cases that were ER-positive and/or PR-positive, HER2-negative and either histologic grade 1 or 2 were classified as Luminal A; cases that were ER-positive and/or PR-positive and HER2-positive, or ER-positive and/or PR-positive, HER2-negative and histologic grade 3 as Luminal B; ER/PR-negative, HER2-positive cases were classified as HER2-type and ER/PR/HER2-negative cases as triple negative. HER2 was considered positive if immunohistochemical stains were 3+ and/or if HER2 FISH showed gene amplification.

**Immunohistochemical analysis**

PDE5A protein was detected using anti-PDE5A antibody diluted 1:100 in real-antibody-diluent (DAKO). Deparaffinization, rehydration, and antigen unmasking were obtained by incubation in tris-phosphate buffer (Envision-Flex-target-retrieval-solution) in a Pre-Treatment Module for Tissue Specimens (PTLINK), following suppliers (DAKO). The staining was performed in a Dako Autostainer-Link48-immunostainer, using a linked streptavidin-biotin technique (Envision Flex kit High pH, DAKO). Sections were counterstained in hematoxylin and coverslipped using DPX mounting medium (Sigma). PDE5 expression/localization were evaluated microscopically by two pathologist independently in a blind fashion. Pictures of representative fields were taken at 20X-magnification using ViewFinder™ Software, through Olympus camera-system dp50. Negative controls showed no staining.