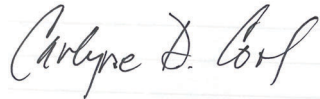


Dear XXXX XXXXX,

Please find the Ignite RPPA Breast Assay report for XXXX XXXXX.

We greatly appreciate your support and look forward to working with you again.

Sincerely,



Carlyne D. Cool, M.D.
Medical Director
Ignite Proteomics

Patient

DOB: XX/XX/XXXX
Sex: Female
MRN: XXXXXXX
Ignite ID: TT26-00012
Diagnosis: Metastatic Breast Cancer

Specimen

Collection Site: Brain Tumor
Specimen Type: Craniotomy
Specimen ID: XXXX-XXXX-XX
Collection Date: XX/XX/XXXX
Received Date: 3/27/2026

Provider

XXXX XXXXX - XXXX XXXXXX XXXXXX, XXXX
XXXX XXXXXX XXXX, XXXXX XXXX, XXXXXXXXXX,
XX XXXXX, Phone: XXX-XXX-XXXX
Test Ordered: XX/XX/XXXX

Hormonal Status

ER: Positive 40%, 3+ | PR: Negative 0% | HER2: Positive (IHC 3+)

ACTIONABLE BIOMARKERS

- HER2
- EGFR^{Y1068}
- HER2^{Y1248}
- SHC^{Y317}
- JAK2^{Y1007 Y1008}
- H2AX^{S139}


THERAPY OPTIONS

 actionable: highly active/expressed  actionable: inactive/not expressed  not actionable: moderately active/expressed

anti-HER2 agent

FDA approved in tumor type

anti-HER2 agent, such as ado-trastuzumab emtansine, fam-trastuzumab deruxtecan-nxki, margetuximab-cmkb, pertuzumab, combination: pertuzumab + trastuzumab + hyaluronidase-zzxf, trastuzumab

supporting biomarkers:  HER2

HER2/HER3 kinase inhibitor

FDA approved in tumor type

HER2/HER3 kinase inhibitor, such as tucatinib

supporting biomarkers:  EGFR^{Y1068}  HER2^{Y1248}  SHC^{Y317}

JAK/STAT3 inhibitor

supporting biomarkers:  JAK2^{Y1007 Y1008}

EGFR/HER2 kinase inhibitor

FDA approved in tumor type

EGFR/HER2 kinase inhibitor, such as lapatinib, neratinib

supporting biomarkers:  EGFR^{Y1068}  HER2^{Y1248}  SHC^{Y317}

PARP inhibitor

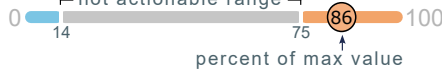
PARP inhibitor, such as olaparib, talazoparib

supporting biomarkers:  H2AX^{S139}

DETAILED RESULTS

LEGEND

mTOR^{Y2448}
↑
activation site



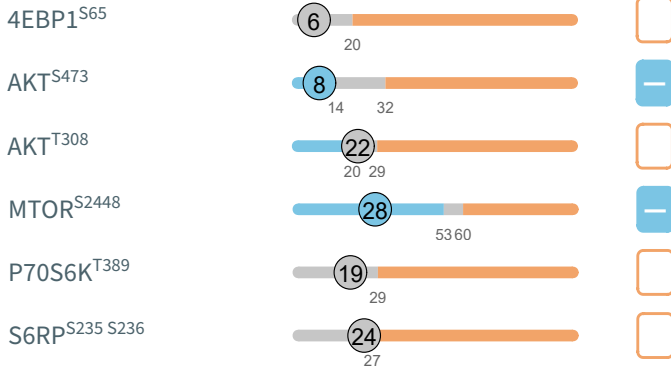
actionable

+ highly active/expressed
- inactive/not expressed

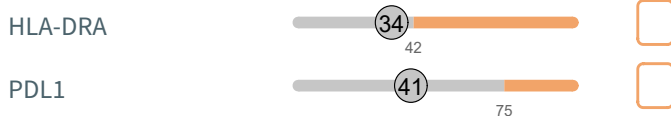
not actionable

moderately active/expressed

PI3K / AKT / mTOR Signaling



Immune Checkpoints Signaling



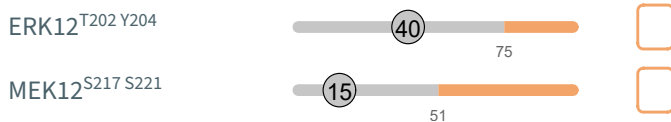
DNA Damage Response



Tumor Microenvironment



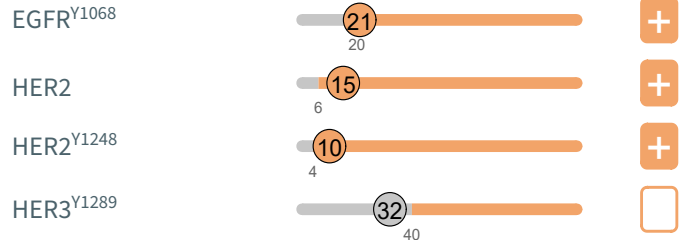
RAS / MEK / ERK Signaling



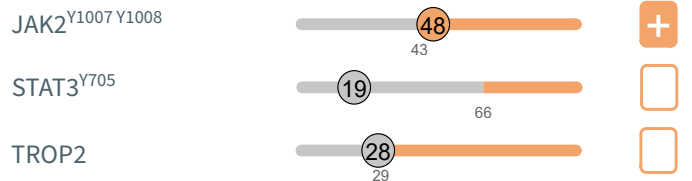
Hormone Receptor



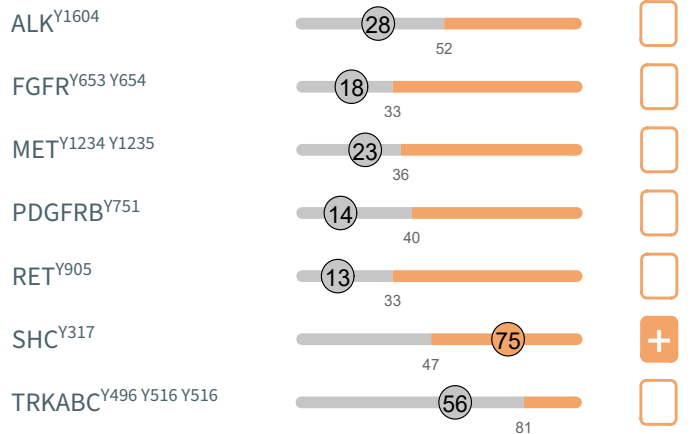
HER2/EGFR Signaling



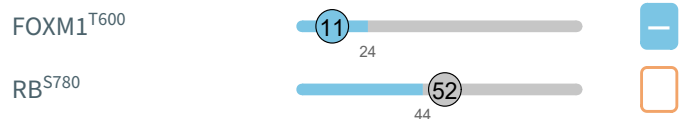
Stem Cell Signaling



Oncogenic RTK



Cell Cycle Regulation



Method: The Ignite RPPA Assay utilizes a Reverse Phase Protein Array (RPPA) methodology to quantify the expression of proteins and phospho-proteins. Individual biomarkers are reported as a percentage of a maximum value that is taken from an Ignite Proteomics reference population of tumor samples. Assay limits of sensitivity for total protein input are ≥ 100 ug/ml and ≤ 400 ug/ml. Limits of sensitivity for individual analytes don't apply due to reporting as percentage.

Individual thresholds are based on expert review of published clinical trial results, scientific literature and population dynamics.

Licensures:

- | | | |
|--------------------------|------------------------|----------------------|
| 1. CAP #8777999 | 4. DC CLIA #HFD-OS7 | 7. PA CLIA #38968 |
| 2. CO CLIA #06D2177270 | 5. MD CLIA #38968 | 8. RI CLIA #LCO01480 |
| 3. CA CLIA #COS-90003315 | 6. NY CLIA #06D2177270 | |

Disclaimer: The Ignite RPPA Assay meets United States standards for performance and quality established by the Clinical Laboratory Improvements Amendments of 1988 (CLIA). The Ignite RPPA Assay is a proprietary protein assay based on Reverse Phase Protein Array technology (RPPA). The assay was developed and its performance characteristics were determined by Ignite Proteomics as a laboratory developed test (LDT). The Ignite RPPA Assay has not been cleared or approved by the US Food and Drug Administration. The results presented herein should be used in conjunction with other patient information under physician guidance and not as only source for treatment decisions.

PI3K/AKT/mTOR Signaling

AKT is a serine/threonine-specific protein kinase group with three isoforms encoded by three different genes: AKT1, AKT2 and AKT3. This group of kinases represent a pivotal component in the PI3K/AKT/mTOR axis of signaling, regulating targets involved in multiple cellular processes such as metabolism, growth, survival, and proliferation (PMID: 15023437; 17604717). Full activation of AKT typically requires phosphorylation at T308 by PDK1, as well as at S473 by mTORC2 (PMID: 8978681; 9094314). Aberrant activity of AKT, via amplification or hyperactivation, has been described in several cancers, even in the presence of normal levels of upstream regulators PI3K and/or PTEN (PMID: 17604717; 16288292; 25309720). One of the most common causes of resistance against ERBB-targeted therapies is directly related to the compensatory overactivation of AKT, making it an important biomarker and promising target for drug development (PMID: 24463007). AKT-specific inhibitors (e.g., MK-2206) are currently in clinical trials (PMID: 33995085). Due to the complex integration of PI3K/AKT/mTOR signaling, and to avoid compensatory signaling, a multi-target inhibitory approach within PI3K, AKT, and mTOR signaling pathways is advisable.

Mammalian target of rapamycin (**mTOR**) is one of the main transducers in PI3K/AKT signaling and regulates metabolism, protein synthesis, cell growth and cell division (PMID: 28283069). mTOR acts as a catalytic subunit in two different protein complexes: mTORC1 (in association with Raptor) and mTORC2 (in association with Rictor). As a response to growth factor signaling and/or other upstream regulators, mTOR is activated via phosphorylation at S2448 (PMID: 19487463; 19145465). Abnormally activated mTOR promotes protein and lipid synthesis and maintains tumor proliferation (PMID: 19948145; 25688110). Like AKT, a multitarget inhibitory approach using mTOR inhibitors (e.g., everolimus, temsirolimus) and PI3K/AKT inhibitors may be beneficial to avoid compensatory signaling.

Eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1) is a direct inhibitor of translation initiation factor 4E (**eIF4E**). It is a downstream component of mTOR signaling, disassociating from eIF4E once phosphorylated at S65 and/or T70 to allow the translation complex to assemble and protein synthesis to take place (PMID: 19339977). Phosphorylated 4EBP1 is a marker of mTOR activity and a potential prognosis indicator, correlating with tumor aggressiveness and poor outcome in both breast and endometrial cancers (PMID: 27026382; 19428047; 17200342).

Both, S6 ribosomal protein kinase (**p70S6K**) and S6 protein (**rpS6**) are downstream effectors of mTOR signaling and, like 4EBP1, play a crucial role in the regulation of protein translation (PMID: 15314020; 15659337). Phosphorylation of p70S6K at T389 is indicative of mTOR activation (PMID: 7489717; 9271440; 9465032) and leads to phosphorylation of rpS6 at multiple residues (e.g., S235, S236). Increased phosphorylation of p70S6K and rpS6 indicate potential sensitivity to PI3K/Akt/mTOR inhibitors (PMID: 22531277; 22213594; 22167413).

Cell Cycle Regulation

The transcription factor Forkhead Box M1 (**FoxM1**) is a key regulator of cell cycle progression, proliferation, differentiation, apoptosis, and angiogenesis, among other processes (PMID: 33680951). This oncogenic protein is a downstream target for several signaling cascades, including MAPK/ERK and PI3K/Akt pathways, and its activity is regulated by multiple posttranslational modifications. Phosphorylation of several residues, including T600, by cyclin-CDK complexes renders FoxM1 active during G2 phase (PMID: 18285455). Like Rb, FoxM1 activity may be indicative of sensitivity to CDK4/6-inhibitors (e.g., palbociclib, abemaciclib and ribociclib), which are standard of care treatment choices for hormone receptor positive breast cancers.

Retinoblastoma protein (**Rb**) is a tumor suppressor that controls cell division by regulating the G1/S transition of the cell cycle. Rb binds E2F transcription factors and acts as a co-repressor of genes necessary for DNA synthesis, thus preventing cell cycle progression. Once phosphorylated by cyclin-CDK complexes, Rb dissociates from E2F, allowing the latter to become active and propel the cell through the S phase (PMID: 10499802; 16936740). CDK4/6-inhibitors are standard of care treatment choices for hormone receptor positive breast cancers (e.g., palbociclib, abemaciclib and ribociclib). Phosphorylated Rb allows assessment of CDK4/6 activation and is therefore a potent indicator of tumor response/therapy resistance to CDK inhibitors (PMID: 24919854; 29050219; 22383795).

EGFR/HER2 Signaling

The transmembrane receptor **HER2** belongs to the human epidermal growth factor receptor (HER/EGFR/ERBB) family and is expressed at low levels to help control cell growth, differentiation, and breast development/maturation. When HER2 forms a dimer—with either another HER2 protein or a different ERBB member—autophosphorylation of tyrosine residues within the intracellular domain triggers proliferative signaling cascades such as the MAPK/ERK and PI3K/Akt/mTOR pathways (PMID: 17471238; 21204711; 31455202). HER2/ERBB2 overexpression/amplification occurs in approximately 20-30% of breast cancer patients. HER2 may also drive tumorigenesis in the absence of overexpression/amplification (i.e. patients who were classified as HER2-negative via IHC/FISH) by over-activation. Phosphorylation of HER2 at Y1248 is a critical marker of HER2 receptor activation that correlates with downstream target activation independently of HER2 expression/amplification status. While increased HER2 signaling is directly associated with a highly aggressive breast cancer subtype, its presence also provides the basis for several HER2-targeted therapies, such as anti-HER2 monoclonal antibodies (e.g., trastuzumab, pertuzumab), and tyrosine kinase inhibitors (TKIs) (e.g., neratinib, lapatinib) (PMID: 2470152; 12897328; 24101045, <https://doi.org/10.1016/j.gendis.2020.12.005>).

HER3 is encoded by the ERBB3 gene, and like HER2, requires dimerization for its activation. However, unlike other ERBB members, HER3 is kinase-impaired and can only be activated via transphosphorylation by a heterodimer binding partner, which is most commonly HER2 (PMID: 8816440; 24269963). Phosphorylation of tyrosine 1289 is a hallmark of HER3 activation and that of its downstream PI3K/Akt/mTOR signaling pathway (PMID: 7929151). HER3 activation has been associated with resistance to EGFR/HER2-targeted therapies as well as endocrine therapies in ER-positive patients. Anti-HER3 antibody treatment in combination with anti-ERBB and/or estrogen-antagonists are showing promising results in multiple studies (PMID: 30057690).

EGFR is one of the most important molecular targets within the ERBB family of receptors. Its overexpression is associated with large tumor size and poor prognosis (PMID: 2884496; PMID: 7612182) and is frequently observed in the more aggressive subtypes of breast cancer: triple-negative breast cancer (TNBC) as well as inflammatory breast cancer (IBC) (PMID: 20164687; 17146782; 2563719). EGFR activates signaling pathways involved in cell proliferation, motility, invasion and angiogenesis, such as MAPK/ERK, PI3K/Akt/mTOR, and PLC- γ 1-PKC signaling (PMID: 22161825; 28513565). Phosphorylation of EGFR at Y1068 is a potent predictor of TKI response. Additionally, phosphorylation at T654 is a hallmark of enhanced receptor stability with a strong correlation with metastasis (PMID: 26247735; 31597954). Small molecule TKI specifically targeting EGFR1 have been FDA approved for breast cancer treatment (e.g., gefitinib, erlotinib) (PMID: 31756933), while monoclonal antibodies against EGFR1 that are currently approved for other cancer types (e.g., cetuximab, panitumumab) are being investigated for their use in breast cancer in clinical trials.

RAS/MEK/ERK Signaling

MEK1/2 activated via phosphorylation at S217/S221 by Raf protein kinases upon growth factor or cytokine stimulation. Once active, MEK1/2 phosphorylate extracellular signal-regulated kinases ERK1/2 at T202/Y204, which in turn activate a collection of downstream kinases and transcription factors that orchestrate cell cycle and survival (PMID: 16393692; 19935650; 17496918). MEK activation has been linked to drug resistance targeting oncogenic EGFR, Ras and Raf, while inhibitors of MEK (e.g., trametinib, selumetinib) alone or in combination with B-Raf inhibitors are showing promising results (PMID: 26399658; 28073102; 28954413; 29488071; 33402199). Similarly, ERK1/2 inhibitors (e.g., SCH772984, ASN007, ravoxertinib) are being considered for their antiproliferative properties even in conditions of resistance to B-Raf and MEK inhibitors (PMID: 34337566; 23614898; 27227380).

DNA Damage Response

Histone **H2AX** undergoes phosphorylation at S139 as part of the DNA repair response to double-strand breakage, which in turn is a major cause of malignant transformation. Elevated phosphorylated H2AX (γ H2AX) is associated with failure of DNA repair and lack of genomic stability that drives tumorigenesis. In breast cancer, higher levels of γ H2AX are associated with greater tumor size, higher grade and the spread to lymph nodes (PMID: 9488723; 26667849; 28158293; 31552812). At the same time, elevated γ H2AX may indicate increased sensitivity to radiation, platinum-based chemotherapies and the combinations of the latter with DNA-repair inhibitors (e.g., FDA approved PARP1 inhibitor, Olaparib) (PMID: 18256616; 30429212; 19005492; 28158293).

Oncogenic RTK Signaling

Fibroblast growth factor receptors (**FGFR**) are a family of receptor tyrosine kinases (RTKs) that promote cell proliferation, survival and migration. In cancer, FGFRs are frequently found aberrantly activated, sometimes due to amplification, gene fusion and hyperactivation (PMID: 8622701; 20094046; 32879300; 33268819). Several multi-target (e.g., pazopanib, ponatinib, regorafenib) and FGFR specific (e.g., erdafitinib, pemigatinib, and infigratinib) TKIs are available that should be considered depending on the signaling pathway activation context (i.e., elevated FGFR activation together with multiple other RTKs versus constitutively activated FGFR) (PMID: 31161538; 34720591; 35494629; doi:10.1038/s42004-021-00623-x).

Like other RTKs, the platelet-derived growth factor receptor beta (**PDGFRb**) gets phosphorylated (e.g., at Y751) upon ligand binding and dimerization, activating other signaling pathways, such as MAPK/ERK and PI3K/Akt. This receptor is known to regulate mesenchymal cells, like fibroblasts and pericytes, and is highly expressed in tumor stroma where it is found to stimulate tumor growth and angiogenesis (PMID: 1284870; 15207817; 18483217). High PDGFRb expression and dysregulated PDGF signaling activity strongly correlate with tumor aggressiveness and shorter survival (PMID: 19498003; 28970051; 29380207; 23583284). Several multi-target TKIs with anti-PDGFRb activity have been approved for cancer treatment (e.g., lenvatinib, regorafenib, pazopanib, sunitinib, ponatinib).

The receptor tyrosine kinase **RET** is activated by glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs) and its subsequent phosphorylation in multiple tyrosine residues (including Y905) results in the activation of downstream signaling pathways, such as MAPK/ERK (PMID: 15982921; 32993133). Oncogenic mutations that result in overexpression and/or constitutive activation of RET are commonly found in several tumor types and are associated with tumor growth, invasion, and metastasis, especially in pancreatic, prostate, and breast cancers (PMID: 30666215). In the context of activated RET, therapy options include multiple small molecule multi-kinase TKIs (e.g., sunitinib, ponatinib, vandetanib, lenvatinib, and sorafenib) and RET-selective inhibitors (pralsetinib and selpercatinib) (PMID: 28911727; 29134959; 3066621; 34497761).

Like other RTKs, **MET** (mesenchymal-epithelial transition factor) plays an essential role in the regulation of cell proliferation, survival and migration (PMID: 21102609). Activation of MET via the ligand hepatocyte growth factor (HGF) and homodimerization results in tyrosine autophosphorylation (i.e., Y1234/Y1235) and the activation of canonical downstream signaling cascades, such as MAPK/ERK, PI3K/Akt and STAT3 pathways (PMID: 11114738; 21102609; 22128289). Aberrant activation of MET — due to mutations and/or crosstalk with ERBB members (e.g., EGFR) — has been found to play a major role in multiple malignancies, including breast, ovarian, liver, lung and pancreatic carcinomas (PMID: 18709663; 22270953). Such dysregulated MET activity has been associated with cancer progression, invasiveness, and therapy resistance, especially in EGFR-dependent cancers (PMID: 17463250; 27450722; 32435640). For instance, EGFR-TKI-resistant/MET-amplified non-small cell lung cancer (NSCLC) patients are showing better results when targeting EGFR in combination with MET (using crizotinib, tivantinib, tepotinib, and cabozantinib, onartuzumab, etc.) or HGF (using ficlatuzumab, rilotumumab, etc.) (PMID: 29621416; 29121501; 31227004; 34322251).

Anaplastic lymphoma kinase (**ALK**) is a RTK that is upstream of several proliferative signaling pathways, such as MAPK/ERK, PI3K/Akt/mTOR, and phospholipase C gamma, among others. Oncogenic ALK signaling is typically found due to genomic rearrangements. The ALK locus is a hot spot for translocation that often results in chimeric fusions with other genes that provide ALK with higher expression rates and constitutive activation (e.g., NPM1-ALK in ALCL and EML4-ALK in NSCLC) (PMID: 24060861; 26384210; 28122866). Phosphorylation of ALK at Y1604 is necessary for its activation and a biomarker of ALK oncogenic signaling as well as a readout for sensitivity to ALK-inhibitors such as alectinib and crizotinib (PMID: 9819383; 17483355; 21847362; 34423228; 34994610).

Shc is an adaptor protein that relays RTK signaling to downstream MAPK/ERK and PI3K/Akt pathways. Shc phosphorylation at Y239, Y240 and Y317 results in recruitment of Grb2/SOS complexes that lead to Ras activation (PMID: 1465135; 18279888; 30210578). Shc is a major mediator of HER2/ERBB signaling, and increased phosphorylation in breast tumors has been associated with poor prognosis, including metastasis and relapse despite tamoxifen therapy (PMID: 9696394; 10741744; 17196107; 18604176; 24407288).

Androgen Signaling

Androgen receptor (**AR**) signaling has been well known for its role in prostate cancer where it has been a critical therapy target. Elevated AR levels have also been seen in other types of cancer, including breast cancer, where it has shown similar tumorigenic properties as well as potential as a therapeutic target, especially in AR-positive, ER-negative/PR-negative breast cancers and TNBC (PMID: 4124279; 23965901; 27816190; 28085048). AR inhibitors have been approved to treat prostate cancer (e.g., bicalutamide and abiraterone acetate) and are currently being tested for their use in breast cancer patients in multiple trials (PMID: 31952272).

Tumor Microenvironment

VEGFR2 is one of the main RTKs responsible for the transduction of angiogenic and vascular permeability signaling. After binding of its cognate ligand VEGF-A and subsequent tyrosine autophosphorylation (e.g., Y951), VEGFR2 activates multiple downstream effectors to promote endothelial proliferation and migration. Some of these effectors include: the PLCgamma/MAPK/ERK proliferative pathway; Src kinases, which regulate cell-to-cell contacts as well as survival via PI3K/Akt; and the SHB/FAK/paxillin axis, which is necessary for focal adhesion turnover and motility (PMID: 16006559; 22866201). VEGF-A/VEGFR2 signaling is one of the main drivers of tumor vascularization, growth and progression, and a major target for anti-angiogenesis therapies (PMID: 12778165; 18463380). Such therapies consist of small molecule inhibitors (e.g., sorafenib, axitinib and pazopanib) as well as monoclonal antibodies targeting VEGF (e.g., bevacizumab) or VEGFR2 (e.g., ramucirumab) (PMID: 26500608; 29508855; 35281942).

Src is a non-receptor tyrosine kinase known for its role in several signaling pathways and a key player in the regulation of cell division, survival, angiogenesis, and adhesion. When phosphorylated (e.g., Y416), this kinase regulates the activity of cadherins, catenins, FAK/Paxillin and Akt, among other effectors (PMID: 18487549; 22153719; 34193161). Increased Src activity strongly correlates with—and most likely contributes to—higher tumor malignancy, invasion, metastasis and TKI resistance (PMID: 6403227; 9014858; 12884910; 15170449; 18487549; 19581523; 21399647). While Src family TKIs are available (i.e. dasatinib), possible associations with immunosuppression warrant careful consideration (PMID: 25662515; 30404626; 34193161).

Paxillin is a downstream signaling adaptor and focal adhesion scaffolding protein with an important role in normal and pathological cell migration. Upon integrin binding and phosphorylation by Src/FAK (e.g., Y118), Paxillin recruits other cotransducer proteins to regulate the adhesion complex dynamics (i.e., assembly versus turnover) and the cytoskeletal rearrangements that are necessary for cell motility (PMID: 28214467; 32859368). Increased Paxillin phosphorylation has been associated with tumor cell growth, migration, invasion and metastasis, and indicates possible responsiveness to Src/FAK inhibitors (PMID: 16360410; 17319853; 23226574).

Stem Cell Signaling

The **JAK2/STAT3** pathway plays a major role mediating cytokine signaling (e.g., IL-6, TNF-gamma) and is found active in both normally developing tissues as well as in multiple cancer types (PMID: 26151455; 31952344; 35241923). JAK2 is a non-receptor tyrosine kinase which is responsible for the phosphorylation of transcription factor STAT3 (i.e., Y705) (PMID: 9111318; 28714740). Activated STAT3 homodimers translocate to the nucleus and promote the transcription of genes that are necessary for cell proliferation, inflammation, survival, metastasis, and epithelial-mesenchymal transition (EMT) (PMID: 17216035; 31952344; 21633165; 27003603; 31308780; 31952344; 32111215). In addition, JAK2/STAT3 activation has been implicated in chemoresistance (e.g., tamoxifen and palbociclib resistance in ER+ breast cancer, resistance to PD-1 blockage).

Trophoblast cell-surface antigen-2 (**TROP2**) is a transmembrane glycoprotein and calcium signal transducer that is commonly found overexpressed in a variety of solid tumor types (including breast), in most cases correlating with poor prognosis and low overall and disease-free survival (PMID: 18813308; 24086649; 26716416; 27645103). TROP2 has become an attractive target for cancer therapies and important marker of treatment sensitivity, and it is particularly promising in triple negative breast cancer (TNBC), where traditional targets are absent. Sacituzumab govitecan is a TROP2-directed antibody and topoisomerase inhibitor drug conjugate that has been approved for use in TNBC patients (PMID: 25915780; 30881031; 33196706; 34116144).

Immune Checkpoints

Programmed death-ligand 1 (**PDL1**) is an immune checkpoint molecule which inhibits T cell activation upon binding to PD1. Under normal conditions, the PDL1/PD1 pathway plays an important role in keeping homeostasis and a proper amount of immune response to avoid pathogenic autoimmunity (PMID: 20636820; 25749122). While PDL1 is normally expressed at low levels in B and T cells, macrophages, and dendritic cells, it can also be found in tumor cells with expression levels that correlate with T cell suppression and tumor immune escape (PMID: 22437870). Breast cancer patients with higher PDL1 expression show more aggressive phenotypes and shorter survival times (PMID: 31359214). The PDL1/PD1 axis has been an important target for the development and use of checkpoint inhibitor immunotherapies, as well as a powerful biomarker to determine which patients will benefit the most from such treatments (PMID: 31336685; 31883913).

HLA-DR is a major histocompatibility complex (MHC) class II antigen presentation molecule, which, together with other MHC-II molecules (HLA-DP and HLA-DQ), presents antigenic peptides obtained from the extracellular environment. The expression of this complex is typically restricted to antigen presenting cells such as dendritic cells, B cells, and macrophages, where it is required for T cell activation and the regulation of adaptive immune responses. However, IFN-gamma stimulation can cause other cell types, such as tumor cells, to produce MHC-II molecules. In tumors, HLA-DR is sometimes highly expressed and associated with higher lymphocytic infiltration as well as better clinical outcomes and indicative of responsiveness to immune checkpoint inhibition (i.e., anti-PDL1/PD) and other immunotherapies (PMID: 2112515; 21281807; 2227249; 3283252; 9301532; 11156321; 30463850).