PET Imaging in Head and Neck Cancer Patients to Monitor Treatment Response: A Future Role for EGFR-Targeted Imaging

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Abstract

Approximately 50,000 new cases of head and neck squamous cell carcinoma (HNSCC) are diagnosed worldwide each year and subsequently treated with surgery, (chemo-)radiotherapy and/or targeted therapy. The heterogeneity of the patient population in terms of treatment response drives the search for tumor specific biomarkers. Imaging of biomarkers can reveal patient-specific responses to therapies and, if assessed early after the start of treatment, may allow adaptation of treatment regimens. In this review, tracers that have been tested to monitor treatment efficacy in HNSCC by PET scanning prior to and early after onset of treatment are discussed. An important imaging target for this application in HNSCC patients is the EGFR. It steers the pathways related to proliferation, hypoxia, DNA damage repair and apoptosis, all treatment resistance mechanisms. The anti-EGFR antibody cetuximab has been labeled with various radionuclides and has been tested as an imaging biomarker in several HNSCC models. These studies suggest that EGFR-targeting tracers can be used to monitor EGFR receptor expression in HNSCC, and have the potential to non-invasively monitor cetuximab treatment and steer individualized treatment regimens. Multiple factors can influence the uptake of EGFR-targeting tracers. Here we discuss the relevance of gene and protein overexpression, mutations and amplifications related to EGFR signaling. In addition, monoclonal antibody properties and the effect on the host immune system are reviewed in light of the future role of EGFR-targeted imaging in HNSCC.
Introduction

For most head and neck squamous cell carcinomas (HNSCC), treatment is with curative intent and consists of surgery and/or radiotherapy, with or without concurrent chemotherapy or targeted therapy. However, approximately 50% of patients with locally advanced disease will develop recurrences or metastases within two years time. Chemotherapeutics like cisplatin and 5-fluorouracil (5-FU) are routinely applied in combination with radiotherapy for treating locally advanced HNSCC, which has shown to have a benefit over radiotherapy alone (1). Targeted therapies are being investigated of which the majority focuses on targeting the EGFR. The EGFR is overexpressed in most epithelial malignancies, including HNSCC, and is involved in pathways related to the tumor microenvironment, tumor cell metabolism and controls cell survival mechanisms such as proliferation, hypoxia resistance, DNA damage repair and apoptosis (2). Cetuximab, a chimeric monoclonal antibody against the EGFR is the only agent approved for use in HNSCC patients. Combining radiotherapy with cetuximab resulted in improved disease free survival (DFS) and overall survival (OS) (3). However, less than 15% of the patients benefit from the addition of cetuximab.

In this review we discuss PET tracers for HNSCC and their potential as imaging biomarkers, focusing on repetitive assessments. The EGFR imaging studies performed so far are reviewed. The strengths and pitfalls of EGFR monitoring, such as receptor expression, mutations and amplifications, are addressed.

Repetitive Imaging in Head and Neck Cancer

The response treatment is influenced by tumor microenvironmental factors like tumor oxygenation, proliferation, as well as intrinsic radioresistance and
acquired drug resistance (4). Microenvironmental differences between tumors can be detected and quantified, for example by determining protein expression profiles by immunohistochemistry. Immunohistochemical analysis is a widely applied technique on biopsy material, however, biopsy sampling is an invasive procedure and prone to sampling errors. Further, repeated biopsy taking is unattractive because anesthesia is often required.

A non-invasive method for biomarker detection is radionuclide imaging using Single-photon emission computed tomography (SPECT) or PET. The strengths of radionuclide imaging are five-fold; 1. It registers the whole tumor in contrast to biopsy studies 2. Multiple lesions may be detected and analyzed simultaneously 3. It targets only those areas that are systemically accessible, representing the accessibility of the drug targets 4. The expression of a specific target of a drug or resistance mechanism can be visualized 5. It allows for repetitive non-invasive assessments. Of special interest are evaluations where PET scans are acquired before and during treatment (Table 1). As such, the patient serves as his/her own control, thereby visualizing and quantifying the effects of the intervention in that particular patient.

**Metabolism**

18F-labeled fluorodeoxyglucose (18F-FDG) is the most widely applied tracer for PET, visualizing tumor cell metabolism. In HNSCC patients, 18F-FDG PET has been used for tumor volume assessment and staging and has prognostic potency as well (5). Hentschel et al showed that the 2-year OS was 88% for patients with ΔSUV$_{\text{max}}$ ≥ 50% measured 1–2 weeks after start of concomitant chemoradiotherapy, relatively to only 38% for patients with ΔSUV$_{\text{max}}$ < 50% ($p = 0.02$) (6). Abgral et al conducted 18F-FDG baseline scans and a second scan after
two cycles of induction chemotherapy, which was then followed by chemoradiation. The median event-free survival (EFS) was 19 months (range 4–25 months) and 10 months (range 8–13 months) for responders and non-responders, which correlated to 1-year EFS rates of 100% and 20%, respectively ($p = 0.0014$) (7). Other studies of similar design have confirmed that a decrease of more than 50% in SUV$_{\text{max}}$ can predict clinical outcome (8, 9). 18F-FDG PET has been tested clinically for a potential role in response monitoring of EGFR-targeting therapies. Schmitz et al reported a partial response to pre-operative administration of cetuximab in eighteen out of nineteen patients, which corresponded to a $\Delta$SUV$_{\text{max}}$ of below -25% as measured at baseline and before surgery (10). A similar design by Adkins et al in ten patients showed that a partial response corresponded to a mean decrease of $\Delta$SUV$_{\text{max}}$ below 48% as measured before and after 8 weeks of cetuximab infusion (11). Though study numbers were limited, 18F-FDG could be further investigated as a potential early marker of cetuximab activity in HNSCC.

Hypoxia

The presence of tumor hypoxia is a common aspect of HNSCC and is a well known cause of resistance to radiotherapy and chemotherapy (12). Hypoxia assessed by means of serial $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO) PET imaging in HNSCC is of prognostic value. Dirix et al showed in 15 HNSCC patients that tumor-to-blood ratios (T/B$_{\text{max}}$) measured before and during chemoradiotherapy correlated negatively to DFS (13). Persistent $^{18}$F-FMISO uptake has also been correlated to locoregional failure (LRF) and local recurrence (LC) (14, 15). $^{18}$F-FMISO imaging and especially dynamic scans could be relevant for response
monitoring, especially with intensity modulated radiation therapy (IMRT), to
guide hypoxic sub-volume delineation for adaptive radiotherapy (16, 17).

$^{18}$F-fluoroazomycin-arabinoside ($^{18}$F-FAZA) accumulates in hypoxic cells
by the same mechanism as $^{18}$F-FMISO. However, it is less lipophilic than $^{18}$F-
FMISO and clears more rapidly from the blood, resulting in improved tumor-to-
background contrast. Mortensen et al showed images with good tumor-to-
background contrast in HNSCC patients as early as 2 h after injection, encouraging further studies (18).

Pretreatment $^{62}$Cu-labeled (diacetyl-bis(N4-methylthiosemicarbazone))
($^{62}$Cu-ATSM), for quantifying hypoxia, showed to have prognostic value as
response to chemoradiotherapy could be predicted by high pretreatment
SUVmax ($> 5.0$) (19). This was supported by another recent study where high
pretreatment $^{62}$Cu-ATSM tumor uptake correlated with a reduced PFS (20).
However, to what extent Cu-ATSM reflects tumor hypoxia is questionable. In a
preclinical study evaluating $^{64}$Cu-ATSM, a negative correlation was found
between hypoxia and tracer uptake in the tumor when assessed at early time
points ($< 16$ h) (21).

**Proliferation**

Tumors with high proliferative activity have shown to be resistant to
chemoradiotherapy (22). A study in 48 HNSCC patients analyzed the change in
proliferation rate with $^{18}$F-labeled 3'-fluoro-3'-deoxy-thymidine ($^{18}$F-FLT) uptake
and found that a SUV$_{\text{max}}$ decrease $\geq 45\%$ between pretreatment and the first 2
weeks of treatment was associated with a significantly better DFS (88% versus
63%, $p = 0.035$) (23, 24). Similar results were obtained by Kishino et al,
confirming the ability of $^{18}$F-FLT to monitor tumor response to chemoradiotherapy (25).

Even though the tracers mentioned above have demonstrated prognostic value, there are many methodological differences influencing study results (21, 26). The potential of these tracers for monitoring targeted therapy response should be more extensively studied in multicenter trials with larger cohorts and improved standardization.

**Potential of EGFR Imaging in Head and Neck Cancer**

**EGFR as a biomarker**

An imaging target in HNSCC is the EGFR, as it is involved in the regulatory pathways in all the radiotherapy resistance mechanisms like hypoxia, proliferation and intrinsic radioresistance (Fig. 1). The EGFR is one of the most dominantly expressed receptors in HNSCC: more than 80% of HNSCC exhibit an increased membraneous expression of this ErbB family member (27). Its natural ligands are growth factors including EGF, TGF-α and heparin-binding EGF-like growth factor (HB-EGF), some being overexpressed in HNSCC as well. EGFR activation steers, amongst others, the EGFR-phosphatidylinositol 3-kinase/protein kinase B (EGFR-PI3K/AKT) and the EGFR-RAS/ERK pathways responsible for DNA repair, proliferation, angiogenesis and inhibition of apoptosis (28-30). The EGFR can also be activated by stress factors like irradiation, and as a consequence, effectors within the hypoxia-inducible factor-1 (HIF-1) pathway can enable tumor cell survival via vascular protection and decreased sensitivity to antioxidant molecules (31). Following activation, the EGFR can be internalized and degraded or recycled back to the cell membrane (32). In addition, the EGFR can be translocated to the nucleus and can regulate
cell proliferation and DNA repair, which has been associated with poor patient outcome (31).

The monoclonal antibodies cetuximab and panitumumab bind to the EGFR and prevent the conformational change in the receptor and thus inhibit dimerization and receptor signaling, subsequently incapacitating tumor cells to overcome radiation damage. Immunohistochemical analyses of EGFR expression in tumor samples produced conflicting results when evaluating its prognostic value (33, 34). A recent meta-analysis in over 3,000 HNSCC patients revealed that EGFR overexpression is correlated to a decreased OS, but not to a decreased DFS. This indicates that other tumor factors and analytical differences play an important role: tumor sites, study regions and scoring system were found to be mostly responsible for the discordance between the studies (35). EGFR expression predicts response to accelerated radiotherapy: a significant benefit in locoregional tumor control was seen in HNSCC patients with high EGFR expression \( (p = 0.01) \) but not in patients with low EGFR expression \( (p = 0.85) \) (36). Similar results were obtained in another large randomized study (37). However, no role for EGFR as a predictive marker for EGFR-inhibitor treatment has been found. In a large clinical trial, no association between immunohistochemical EGFR status and cetuximab benefit was found (38). In addition, in HNSCC the EGFR gene copy number did not correlate with cetuximab response (39-41).

**EGFR imaging**

In the search for potential imaging biomarkers, cetuximab and cetuximab analogues have been labeled with several PET radionuclides including \( ^{124}\text{I}, \ ^{64}\text{Cu}, \ ^{89}\text{Zr}, \text{and} \ ^{86}\text{Y} \) (42). Most studies so far were carried out in animal models. In 2005,
Perk et al labeled cetuximab with $^{89}$Zr, $^{88}$Y, and $^{177}$Lu and found that the biodistribution of the radiolabels in mice with A431 xenografts was similar (43). Several studies showed that $^{89}$Zr-cetuximab tumor uptake correlated with EGFR expression determined immunohistochemically (44, 45). Aerts et al found a discrepancy as intermediate EGFR expressing tumors had a higher uptake of $^{89}$Zr-cetuximab than those with high EGFR expression. This was most likely due to the use of an EGFR saturating protein dose of the tracer in these models (100 µg/mouse) (46). $^{89}$Zr-cetuximab dosimetry has recently been studied in colorectal patients, showing that the liver received the highest absorbed dose of $0.61 \pm 0.09 \text{ mSv} \cdot \text{MBq}^{-1}$ (47). The ultimate aim is to apply these tracers for treatment monitoring and response prediction. In addition, anti-EGFR tracers could potentially aid in determining nodal metastatic disease. Treatment monitoring using repetitive imaging has been studied in HNSCC xenografts with $^{111}$In-labeled cetuximab-F(\text{ab'})$_2$. This tracer could visualize changes of EGFR expression and tumor uptake was correlated with response to the combination of irradiation and cetuximab (48, 49). In addition, a reduced uptake of $^{111}$In-cetuximab-F(\text{ab'})$_2$ in the post-treatment scan compared to the pre-therapy scan correlated with response to treatment, while resistance to therapy was characterized by a significantly increased $^{111}$In-cetuximab-F(\text{ab'})$_2$ tumor uptake. The rapid kinetics of F(\text{ab'})$_2$ tracers and the promising preclinical results, indicate that this tracer has potential clinical value and should be further investigated.

**Considerations**
Multiple factors can influence the uptake of EGFR-targeting tracers. Response to cetuximab treatment and the correlation with EGFR-tracer uptake can be differentially affected by tumor and host microenvironmental factors.

**Overexpression, mutations and amplifications**

There are EGFR alterations present in HNSCC, such as EGFR overexpression and increased EGFR gene copy number (40, 41). Even though the EGFR expression level has prognostic value, EGFR-inhibition efficacy depends on factors affecting downstream signaling (31). The EGFR can be bypassed due to dependency on other ErbB pathways, the receptors of which are also known to be overexpressed in HNSCC, albeit usually to a lesser extent than EGFR (50). EGFR-independent pathways can support tumor growth, for example, through activation of several other G protein-coupled receptors (GPCR). These GPCR can activate AKT and ERK via protein kinase C (PKC) or activate the EGFR tyrosine kinase in an tyrosine-protein kinase CSK (Src)-dependent manner, resulting in continued tumor cell proliferation (51). In addition, cetuximab ineffectiveness can be related to mutations in the downstream signaling cascade of the EGFR. For example, the PIK3CA gene encoding for the p110-alpha subunit of P13K is often amplified in HNSCC and promotes cellular proliferation (52). In addition, the tumor suppressor protein p53, as in many other cancers, is mutated in the majority of HNSCC and also influences tumor proliferation (53).

A number of studies have investigated EGFRvIII, the truncated constitutively active EGFR variant III (54). It harbors mutations in the extracellular binding domain and influences monoclonal antibody binding, thereby affecting inhibition of downstream signaling pathways (55). Recently, a large study by Khattri et al, evaluated EGFRvIII expression in 638 HNSCC
samples, and found that less than 0.4% of the tumors were EGFRvIII-positive, indicating that the role of EGFRvIII in HNSCC is limited (56).

**Immune response mechanisms**

The antibody-dependent cellular cytotoxicity (ADCC) that cetuximab supposedly elicits has gained considerable interest (57). The fragment crystallizable (Fc) region of an immunoglobulin G1 (IgG1) antibody can bind several immune cells via the antibody-binding receptor FcγRIIIa on natural killer cells, dendritic cells, monocytes or other granulocytes. This initiates the release of specific enzymes that could degrade the tumor cells it is bound to (58). If ADCC is a significant contributor to tumor response in cetuximab treatment, results obtained in preclinical research may not be representative for the clinical situation as there is no adaptive immunity that can generate a specific immune response in murine xenograft models due to the lack of T cells in these animals. Recently, it has been shown that EGFR-specific T-lymphocytes in cetuximab-treated HNSCC patients may contribute to anti-tumor activity relevant to clinical response (59). Therefore, the effect of cetuximab can be underestimated by absence of adaptive ADCC-driven tumor cell kill in xenograft models.

Another characteristic of EGFR-targeting tracers is that they bind to EGFR expressed on normal tissues as well. As the EGFR is present in many normal human epithelial tissues, it can elicit a multitude of side effects (60). In the skin, EGFR inhibition deregulates normal keratinocyte proliferation, differentiation and migration, resulting in an acniform rash (61). In HNSCC patients, a correlation between the intensity of cutaneous rash and the effectiveness of cetuximab has been suggested (62). The interaction between rash and cetuximab response is currently under further investigation in a phase IV trial.
(NTC01553032) (63). If confirmed, the severity of skin rash may aid in selecting patients for less toxic regimens (i.e. radiotherapy with cetuximab) or more intense regimens (i.e. chemoradiation).

Treatment with monoclonal antibodies can elicit immunological human anti-mouse antibody responses (HAMA) in patients, which subsequently can evoke allergic reactions and reduce monoclonal antibody efficacy (64). This was primarily seen in the first generation antibodies of murine origin. Chimeric antibodies like cetuximab contain less murine epitopes, but might still instigate a HAMA response and/or hypersensitivity reaction (65). Panitumumab targets the EGFR and is a fully human IgG2 monoclonal antibody, which therefore does not evoke a HAMA response. However, panitumumab could still induce a human anti-human antibody (HAHA) formation and hypersensitivity reactions because of a higher amount of effector T-cell epitopes and smaller number of immune suppressing regulatory T-cell epitopes on the engineered antibody (66). Panitumumab is currently used to treat colorectal cancer (67). In addition, 89Zr-panitumumab is currently tested clinically as an EGFR monitoring tracer in HNSCC (68).

Properties of monoclonal antibodies

Cetuximab has a half-life of 95 ± 24 hours in humans (69). If used as an imaging agent, it is present in the circulation for weeks, impeding rapid serial imaging. In mice, cetuximab has a half-life of ca. 40 hours and optimal images with 111In-labeled cetuximab can be acquired 3 – 7 days after injection (32, 70). To facilitate earlier imaging and allow quick repeated assessments, the use of radiolabeled F(ab’)2 Fab’ fragments or other small formats of cetuximab might be a solution (71, 72). These fragments exhibit rapid clearance from the blood and rapid
tumor penetration, while retaining the affinity of cetuximab IgG (71, 73). Especially in relation to monitoring treatment regimens, it would be an advantage if early repeated imaging would enable earlier adaptation of the therapeutic regimen. In addition, tumor cells can exhibit rapid turnover, especially in hypoxic tumors (< 49 h) (74). Hence, rapid assessment with antibody fragments could more accurately reflect receptor expression. This is in contrast to intact IgG tracers, which require delayed imaging for optimal tumor-to-background contrast and thus could potentially overestimate EGFR targetability.

As cetuximab is administered in relatively high doses for treatment purposes, application of an EGFR tracer directed against the same epitope is not possible during cetuximab treatment due to EGFR saturation. Therefore, the timing of image acquisition in relation to the administered therapeutic dose is essential.

**Conclusion**

For treatment response monitoring, agents such as $^{18}$F-FDG and proliferation- or hypoxia related tracers have been used. Radiolabeled EGFR-inhibitors like cetuximab have great potential to assess EGFR receptor expression before and during treatment. Clinical research works towards a role for these tracers to monitor treatment response, thereby allowing adaptation of treatment regimens when necessary. Current and future studies will demonstrate the effectiveness of such strategies in the HNSCC patient population and ultimately could enable individualized treatment.

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References


the HICARE protocol (head and neck cancer: immunochemo and radiotherapy with erbitux) - a multicenter phase IV trial. BMC Cancer 2013;13:345.


**Table 1.** PET tracers studied for response monitoring in HNSCC

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Author, year (reference no.)</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>Scoring</th>
<th>Time of second scan</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F-FDG</td>
<td>Hentschel et al, 2011 (ref 6)</td>
<td>37</td>
<td>CRT</td>
<td>SUV$_{\text{max}}$ decrease $\geq$ 50%</td>
<td>$&lt;$ 2 weeks of CRT onset</td>
<td>OS ($p = 0.02$)</td>
</tr>
<tr>
<td></td>
<td>Abgral et al, 2012 (ref 7)</td>
<td>15</td>
<td>ICT/CRT</td>
<td>SUV$_{\text{max}}$ decrease $\geq$ 25%</td>
<td>8 weeks after ICT</td>
<td>EFS ($p = 0.0014$)</td>
</tr>
<tr>
<td></td>
<td>Yoon et al, 2011 (ref 8)</td>
<td>21</td>
<td>ICT/CRT</td>
<td>SUV$_{\text{max}}$ decrease $\geq$ 65%</td>
<td>2 - 4 weeks after ICT onset</td>
<td>CR ($p = 0.003$), PFS ($p &lt; 0.001$), OS ($p = 0.001$)</td>
</tr>
<tr>
<td></td>
<td>Klaeser et al, 2009 (ref 9)</td>
<td>45</td>
<td>ICT/CRT + surgery</td>
<td>SUV$_{\text{max}}$ decrease $\geq$ 50%</td>
<td>5 weeks after ICT onset</td>
<td>Histological complete or near-complete response on biopsy ($p = 0.021$)</td>
</tr>
<tr>
<td></td>
<td>Schmitz et al, 2013 (ref 10)</td>
<td>32</td>
<td>Cetuximab + surgery</td>
<td>SUV$_{\text{max}}$ decrease $\geq$ 25%</td>
<td>1 day before surgery</td>
<td>PR in 95% of patients</td>
</tr>
<tr>
<td></td>
<td>Adkins et al, 2014 (ref 11)</td>
<td>27</td>
<td>Cetuximab</td>
<td>SUV$_{\text{max}}$ decrease $\geq$ 48%</td>
<td>8 weeks after cetuximab</td>
<td>PMR in 37% of patients (range $-24%$ to $-81%$)</td>
</tr>
<tr>
<td>$^{18}$F-FMISO</td>
<td>Dirix et al, 2009 (ref 13)</td>
<td>15</td>
<td>CRT</td>
<td>T/B$_{\text{max}}$ $\geq$ 1.17</td>
<td>3 weeks after CRT onset</td>
<td>DFS ($p = 0.02$)</td>
</tr>
<tr>
<td></td>
<td>Rischin et al, 2006 (ref 14)</td>
<td>45</td>
<td>CRT</td>
<td>Qualitatively according to baseline scan - persistent uptake</td>
<td>4 - 5 weeks after CRT onset</td>
<td>LRF ($p = 0.038$)</td>
</tr>
<tr>
<td>$^{62}$Cu-ATSM</td>
<td>Zips et al, 2012 (ref 15)</td>
<td>25</td>
<td>CRT</td>
<td>TBR$_{\text{max}}$ $\geq$ 1.93</td>
<td>2 weeks after CRT</td>
<td>LPFS ($p = 0.001$)</td>
</tr>
<tr>
<td>Minagawa et al, 2011 (ref 19)</td>
<td>15</td>
<td>CRT</td>
<td>SUV$_{\text{max}}$ $\geq$ 5.0</td>
<td>Prior to CRT</td>
<td>Histological complete response ($p &lt; 0.05$)</td>
<td></td>
</tr>
<tr>
<td>Sato et al, 2014 (ref 20)</td>
<td>25</td>
<td>CRT + surgery</td>
<td>SUV$_{\text{max}}$ $\geq$ 3.6</td>
<td>Prior to CRT</td>
<td>PFS ($p = 0.047$)</td>
<td></td>
</tr>
<tr>
<td>$^{18}$F-FLT</td>
<td>Hoeben et al, 2013 (ref 24)</td>
<td>48</td>
<td>CRT</td>
<td>SUV$_{\text{max}}$ decrease $\geq$ 45%</td>
<td>2 weeks after RT onset</td>
<td>DFS ($p = 0.035$)</td>
</tr>
<tr>
<td>Kishino et al, 2012 (ref 25)</td>
<td>28</td>
<td>CRT</td>
<td>Qualitatively according to baseline scan - absence of uptake</td>
<td>4 weeks after RT onset</td>
<td>Endoscopic, radiographic, pathologic response ($p &lt; 0.0001$)</td>
<td></td>
</tr>
</tbody>
</table>
CRT: chemoradiotherapy; ICT: induction chemotherapy; SUV\textsubscript{max}: maximum standard uptake value; T/B\textsubscript{max}: maximum tumor-to-blood; EFS: even free survival; OS: overall survival; LRC: locoregional control; CR: complete response; PR: partial response; PMR: partial metabolic response; PFS: progression free survival; DFS: disease free survival; LRF: locoregional failure; LPFS: local progression free survival
**Figure 1.** Mechanism of EGFR-mediated downstream signaling.

Orange oval: natural ligands; red text: competing inhibitory antibodies; green circles: intracellular signaling pathways, blue circle: nucleus.

Figure 1:

EGF  
TGF-α  
HB-EGF  
Cetuximab  
Panitumumab  
Zalutumumab

EGFR

Extracellular

Intracellular

PLC  
PI3K  
JAK  
RAS  
PLC  
PI3K  
JAK  
RAS

PKC  
AKT  
STAT  
SRC  
PKC  
AKT  
STAT  
SRC

RAS  
RAF  
MEK  
mTOR  
MAPK  
ERK  
RAS  
RAF  
MEK  
mTOR  
MAPK  
ERK

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