# Ion Channels and Cancer

**An updated overview**

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During the last few years a pivotal role for ion channels involvement in cancer has emerged. In Modulator #17, we reviewed examples of possible roles and interplay between ion channels and cancer (posted on our website www.alomone.com). Recently, a large body of data has accumulated on the participation of K⁺, Na⁺, Ca²⁺, Cl⁻ and ligand-gated channels in cancer and apoptosis. To date, there is no broad consensus on the roles ion channels play in cancer. Ion channels are thought to “assist” cancer by affecting a number of pathways, namely, regulation of cell cycle of proliferating cells, perturbation of membrane potential, prevention of apoptosis, adaptation to harsh conditions, altering intracellular Ca²⁺ balance, and cell shrinkage. Interestingly, there are some examples of the same ion channel participating both in induction of cancer cell proliferation and in induction of apoptosis, for example Kᵥ11.1 (HERG) and Kᵥ9.1 (TASK3) K⁺ channels. Furthermore, the hallmark of certain cancers is the upregulation of a particular channel or conversely, its total absence, as has been reported for voltage-gated Na⁺ channels. This accumulating data predicts that ion channels will possibly be future targets for diagnostics and therapeutics in cancer.

<table>
<thead>
<tr>
<th>Channel Type</th>
<th>Cancer Involved</th>
<th>Up/Down</th>
<th>Activity</th>
<th>Related Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage-Dependent Na⁺ channel</td>
<td>Prostate</td>
<td>↑</td>
<td>Upregulated in metastatic MATLyLu vs. AT-2 cells. Cell motility reduced in the presence of VGSC blockers and increased with VGSC openers. The authors propose that the channel involved is Naᵥ1.7.6</td>
<td>Anti-Naᵥ1.7, ASC-008 Anti-Pan Naᵥ, ASC-003</td>
</tr>
<tr>
<td>Naᵥ1.2</td>
<td>Prostate</td>
<td>↑</td>
<td>Use of specific Naᵥ (mainly Naᵥ1.2) blockers from the hydroxyamides and hydantoin families have shown remarkable inhibition in cell growth of the androgen-independent PC-3 cell line.7</td>
<td>Anti-Naᵥ1.2, ASC-002 Anti-Pan Naᵥ, ASC-003</td>
</tr>
<tr>
<td>Naᵥ1.4</td>
<td>Prostate</td>
<td>↑</td>
<td>Upregulated in invasive androgen-insensitive cell lines. Tumor invasion reduced in the presence of TTX.⁴</td>
<td>Anti-Naᵥ1.4, ASC-009 Anti-Pan Naᵥ, ASC-003</td>
</tr>
<tr>
<td>Naᵥ1.6</td>
<td>Glioma</td>
<td>↓</td>
<td>Higher-grade gliomas express fewer Na⁺ channel subtypes and at lower levels than low-grade tumors. Naᵥ1.6 was almost absent in gliomas, unlike in normal tissue.⁵</td>
<td>Anti-Naᵥ1.6, ASC-007</td>
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<tr>
<td>Kᵥ1.3</td>
<td>Breast</td>
<td>↑</td>
<td>A marked expression is observed in breast cancer specimens and cell lines. The Kᵥ1.3 opener Minoxidil has stimulated growth, while K-channel blocker amiodarone had a marked inhibitory effect on MCF-7 proliferation.⁶</td>
<td>Anti-Kᵥ1.3, APC-002 Anti-Kᵥ1.3, APC-010 Anti-Kᵥ1.3, HRTC-APC101-F</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
<td>↑</td>
<td>Kᵥ1.3 expression was up-regulated in a number of colon specimens and cell lines. K⁺ channel openers increased cell growth, while blockers caused a marked inhibition in cellular proliferation of a number of cell lines.⁷</td>
<td>Anti-Kᵥ1.3, ASC-001 Anti-Kᵥ1.3, ASC-002</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>↑</td>
<td>Kᵥ1.3 expression is found in prostate cancer specimens and cell lines. Kᵥ1.3 opener increased growth of PC3 cells by 50-50%, while K⁺-channel blockers had marked inhibitory dose-dependent effect on PC3 proliferation.⁸</td>
<td>Anti-Kᵥ1.3, ASC-001</td>
</tr>
<tr>
<td>Kᵥ1.5</td>
<td>Glioma</td>
<td>↓</td>
<td>Kᵥ1.5 expression correlated with glioma entities and malignancy grades, namely expression was high in astrocytomas, moderate in oligodendrogliomas, and low in glioblastomas.⁹</td>
<td>Anti-Kᵥ1.5, ASC-004</td>
</tr>
<tr>
<td>Kᵥ3.4</td>
<td>Oral Squamous Cell Carcinoma</td>
<td>↑</td>
<td>Over-expressed in OSCC tissues. 4-aminopyridine and specific ODN (phosphorothionate oligodeoxylnucleotide)-antisense against Kᵥ3.4 in OSCC cells resulted in significant growth inhibition.¹⁰</td>
<td>Anti-Kᵥ3.4, ASC-003</td>
</tr>
<tr>
<td>Kᵥ5.1 (BK, Slo)</td>
<td>Glioma</td>
<td>↑</td>
<td>Over-expressed in higher-grade tumors and glioma cell lines. Iberiotoxin, a BK-specific blocker was shown to inhibit the migration of U-251MG glioma cells in vitro.¹¹</td>
<td>Anti-Kᵥ5.1, ASC-002 Anti-Kᵥ5.1, ASC-008</td>
</tr>
<tr>
<td>Kᵥ3.1 (IK Intermediate Ca²⁺-activated K⁺ Channel)</td>
<td>Prostate</td>
<td>↑</td>
<td>1-EBIO and riluzole induced PC-3 and LNCaP proliferation, which was inhibited by IK blockers, such as Charybdotoxin and clotrimazole. BK and SK blockers had no effect under the same conditions.¹²</td>
<td>Anti-Kᵥ3.1, ASC-004</td>
</tr>
<tr>
<td>Kᵥ11.1 (HERG)</td>
<td>Colon</td>
<td>↑</td>
<td>HERG1 is highly expressed in colorectal cancer cell lines, as compared with non-cancerous tissues. Furthermore, HERG1 plasma membrane expression is directly related to the invasive phenotype of colon cancer cells.¹³ HERG is frequently expressed in endometrial cancer, as compared with non-cancerous tissues.¹⁴ Expression of HERG1 and HERG1B was found in Neuroblastoma SH-SY5Y cells. Blocking HERG channels dramatically impairs cell growth.¹⁵-²⁰ HERG appears to be constitutively active in Leukemic cell lines, and their proliferation altered in the presence of E-4031, a selective HERG channel blocker.¹⁶²⁰</td>
<td>Anti-Kᵥ11.1, ASC-006 Anti-hKᵥ11.1, ASC-016</td>
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<tr>
<td></td>
<td>Endometrial cancers</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>Channel Type</td>
<td>Tissue</td>
<td>Effect</td>
<td>References</td>
<td></td>
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<tr>
<td>Ca^2+ permeable non-selective cation channels NSCC-1 NSCC-2</td>
<td>Prostate</td>
<td>↑</td>
<td>References</td>
<td></td>
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<tr>
<td>TRPV6 (Cat1)</td>
<td>Prostate</td>
<td>↑</td>
<td>References</td>
<td></td>
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<tr>
<td>TRPC1</td>
<td>Prostate</td>
<td>↑</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>TRPM8 (TRPP8)</td>
<td>Breast, Colon, Ovarian, Prostate, Thyroid</td>
<td>↑</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>Cl Channels</td>
<td>Breast, Cervical, Hepatoma, Glioma, Nasopharyngeal, Squamous cell lung carcinoma, Pancreas, Prostate</td>
<td>↑</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>ASIC</td>
<td>Glioma</td>
<td>↑</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>Purinergic P2X non-selective ion channels</td>
<td>Leukemia Neuroblastoma Skin</td>
<td>↑</td>
<td>References</td>
<td></td>
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</tbody>
</table>

References:
Related Anticancer Antibiotics

17-AAG inhibits cell proliferation. HeLa (●) cells were grown in the presence of different concentrations of 17-AAG for 4 days then the cell quantity was measured using the Methylene blue method. The cell quantity versus 17-AAG concentrations are presented in the figure.

Geldanamycin inhibits cell proliferation. HeLa (●) and Jurkat (▲) cells were grown in the presence of different concentrations of Geldanamycin for 4 days then the cells quantity was measured using the XTT or Methylene blue method. The cell quantity versus Geldanamycin concentrations are presented in the figure.

Radicicol inhibits cell proliferation. HeLa (●) WEHI (▲) and Jurkat (▲) cells were grown in the presence of different concentrations of Radicicol for 4 days then the cell quantity was measured using the Methylene blue or XTT method. The cell quantity versus Radicicol concentrations are presented in the figure.