Tentative Outline

Special Thematic Issue for the journal Current Molecular Pharmacology

Title of the Thematic Issue: "An In-dire-need of a specific Notch2 agonist/antagonist to treat human cancer and tissue-defects"

Guest Editor: Dr. Shiv Kumar

- **Scope of the Thematic Issue:**

Notch signaling plays countless roles in development, homeostasis, regeneration, and disease. With its function in direct cell-to-cell communication, cell lineage specification, and differentiation, stem cell maintenance, migration, proliferation, and survival. The canonical Notch2 signal pathway needs Notch ligands (DLL and Jagged) binding to lead nuclear localization of the Notch intracellular domain (NICD) followed by sequential protease (Adam and gamma-secretase) cleavages of Notch receptors. In the nucleus, NICD binds to RBPJ (CSL) and Maml1 and forms a transcriptional ternary complex to activate downstream signaling, including Sox9 and Hes1 induction. The aberrant regulation of the Notch2 pathway results in tumorigenesis and inborn errors and defects. The upregulated Notch2 signaling has led to different types of cancer progression like Melanoma, CLL, lung cancer, metastasis-pancreatic cancer, gastric, glioblastoma, and breast cancer. Although several Notch inhibitors (Not directly targeting Notch2 receptor), DAPT, LY3039478, MRK560, RG473, CT16, Brontictuzumab, Anti-NRR1/2, Enoticumab, Tarextumab, ABT165, IMR1, RIN1, SAHM1, CB103, etc., have been discovered and are running in different phases of clinical trials with toxicities, like diarrhea, hypercapnia, Fatigue, Anemia, thrombocytopenia, and metaplasia, etc., Among all, 90% of known inhibitors inhibit one of these factors, either Notch ligands activity or y-secretase or Transcriptional complex (RBPJ/NICD/Maml1), and consider Pan-notch inhibitors. In the current scenario, a specific, safe, and direct Notch2 inhibitor (Not a Pan-Notch inhibitor) is far awaited to be explored for therapeutic use specifically for Notch2-associated diseases. Apart from this, the downregulated Notch2 implicates chondrosarcoma and breast cancer progression. Further, overexpressed Notch2 inhibits chondrosarcoma and breast cancer progression. The failure of Notch2 activation due to heterozygous loss of *JAG1* causes pleiotropic defects in numerous organ systems like the liver, heart, eyes, spine, etc. The inactivation of Notch2 results in Alagille syndrome (ALGS) and Biliary Atresia (BA) in the liver, cardiac ventricular septum defects in the heart, spina bifida, etc. ALGS occurs in every 35,000 births and is caused by heterozygous loss of the Notch ligand gene, *JAGGED1*, leading to a neonatal paucity of liver ducts. Failure of hepatic duct regeneration consequently leads to liver dysfunction and 76% lethality by late adolescence. JAGGED/NOTCH signaling regulates the development and regeneration of many tissues, including liver ducts, heart ventricular chamber separation, eyes, and spine. Recent *in vivo* studies revealed that increasing Jagged/Notch signaling enhances liver duct regeneration in *jagged* mutant models of Alagille Syndrome, implicating Notch signaling increase as a viable therapeutic strategy. However, there are currently no standard small-molecule Notch2 agonists discovered yet.

This insight is critical to optimize new small-molecule screening and testing Notch2-dependent agonists and antagonists to target different cancers and JAGGED1 loss diseases like ALGS, BA, Cardiac septum defects, spina bifida, craniofacial defects, mental retardation, etc.

In this special issue, we will accumulate the evidence and small molecules that directly binds to and modulates Notch2 activity to treat Notch2-associated diseases.

Keywords: Notch2 signaling, Agonist, antagonist, Liver disease, Cardiac defects, Cancers.

Sub-topics:

- Identification of Notch2 signaling modulator.
- Characterization and specificity Notch agonist/antagonist
- Notch downstream signaling activation.
- Targeting of Notch-associated diseases

Tentative titles of the articles:

- Small molecule activates Notch2/SOX9 signaling and leads to intrahepatic duct regeneration.
- Small Molecule activates Notch2/Sox9 signaling to treat cardiac ventricle septum defects.
- Small molecule regenerates ducts in a Jag1 knockout mouse liver in Notch2-dependent manner.
- Small molecule-mediated activation of Notch inhibits chondrosarcoma progression.
- Small molecule activates Notch signaling to inhibit breast cancer.
- Small molecule inhibits pancreatic cancer metastasis in a Notch2-dependent manner.
- Small molecule inhibits glioblastoma metastasis via inhibiting notch signaling.

Schedule:

- Thematic issue submission deadline: **31 March 2024**

Contacts:

Guest Editor's Name: Dr. Shiv Kumar

Affiliation: Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA-USA-92037

Email: skumar@sbpdiscovery.org; ars198922@gmail.com