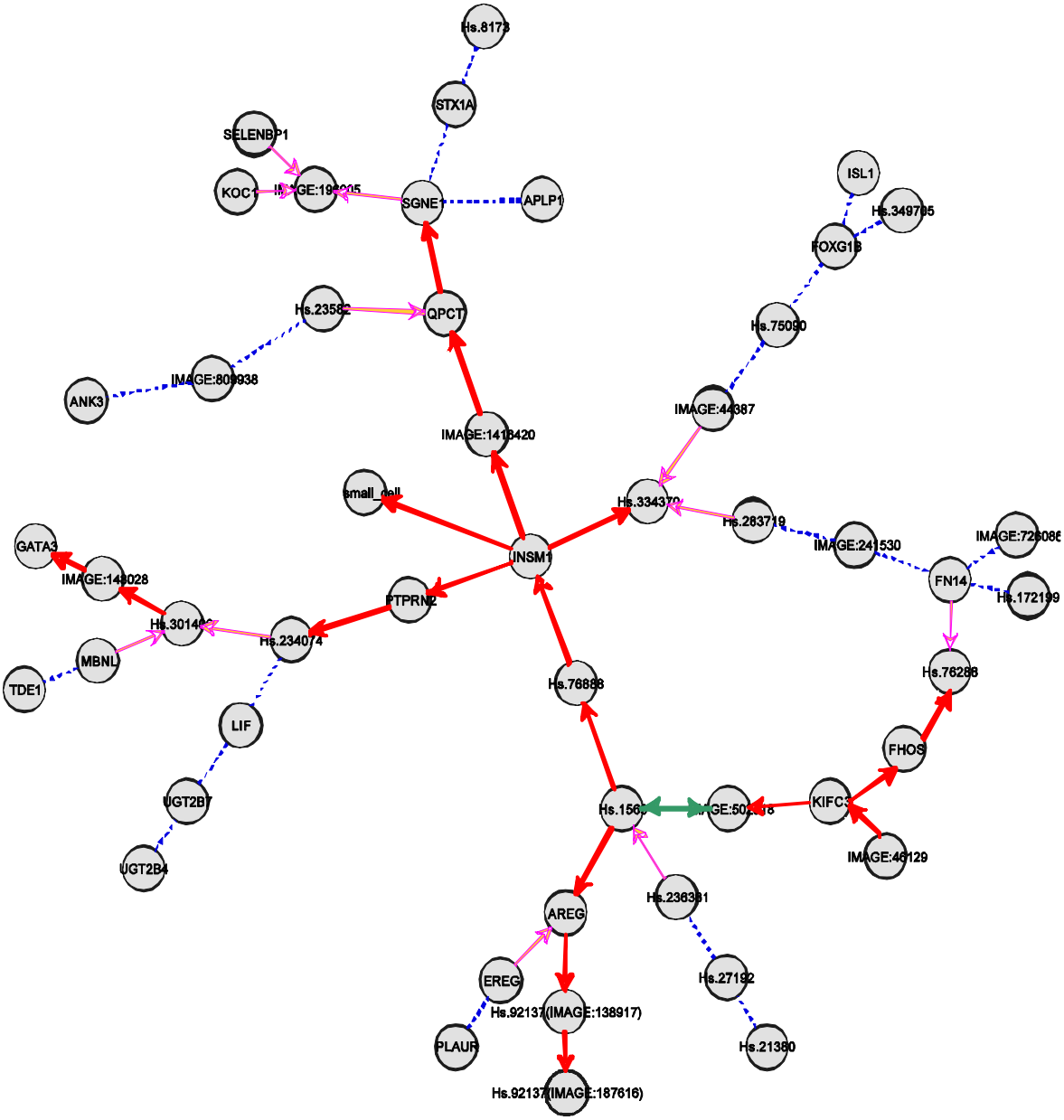


Supplemental Figure: The 'small cell' sub-network. Bold red directed edges are of type −−>, simple pink directed edges o−>, bold green bidirected edges <−>, and dotted blue undirected edges o−o.

## Locuslink annotations

**INSM1** (insulinoma-associated 1): **marker for lung tumours of neuroendocrine differentiation**; zinc finger DNA-binding domain + putative prohormone domain (transcription regulator)
**IMAGE:1416420 (ASCL1)**: neuronal differentiation marker achaete-scute homolog; basic helix-loop-helix family of TFs; neuronal commitment and differentiation and in the generation of olfactory and autonomic neurons; **highly expressed in small cell lung cancer; may be a useful marker for this cancer**
**QPCT**: glutaminyl cyclase; posttranslational modification of neuropeptide precursors
**Hs.23582 (TACSTD2)**: tumor-associated calcium signal transducer 2; epithelial glycoprotein-1; Thyroglobulin type-1 repeat; encodes a carcinoma-associated antigen member of a family including at least two type I membrane proteins. It transduces an intracellular calcium signal and acts as a cell surface receptor; biological process: cell proliferation.
**IMAGE:809938 (TACSTD2)**

**SGNE1 (7B2)**: Secretory granule, neuroendocrine protein 1; specific chaperone for proprotein convertase-2 (PC2 - endoprotease involved in the processing of neuroendocrine precursors); localizes to secretory granules containing peptide hormones.
**PTPRN2**: Protein tyrosine phosphatase, receptor type, N polypeptide 2; extracellular region + transmembrane region + intracellular catalytic domain. (PTPs are signaling molecules regulating a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation.)
**Hs.234074 (DNER)**: Delta-notch-like EGF repeat-containing transmembrane protein; expressed in the developing and mature central nervous system, especially during formation of dendrites and axons; has a single transmembrane region.
**LIF**: Leukemia inhibitory factor (cholinergic differentiation factor); cytokine that regulates growth and differentiation of a wide variety of cells in the adult and the embryo. LIF signals through different receptors and TFs.
**IMAGE:148028 (EPS8)**: Epidermal growth factor receptor pathway substrate 8; has a role in normal and neoplastic cell proliferation.
**GATA3**: GATA binding protein 3; Zinc-finger TF (enhancer binding); embryogenesis and morphogenesis
**MBNL**: muscleblind-like (Drosophila).
**TDE1**: tumor differentially expressed 1; integral to membrane
**STX1A** Syntaxin 1A (brain): involved in intracellular transport and neurotransmitter release; regulates CFTR (cystic fibrosis transmembrane conductance regulator) activity in airway epithelial cells.
**APLP1** amyloid beta (A4): precursor-like protein 1; heparin binding; cell adhesion; endocytosis; histogenesis and organogenesis; neurogenesis; apoptosis; coated pit; basement membrane; integral to membrane.
**IMAGE:196005 (AQP3)**: Aquaporin 3 is a water channel protein.
**KOC1**: IGF-II mRNA-binding protein 3; KH domain containing protein overexpressed in cancer. The protein encoded by this gene is primarily found in the nucleolus, where it can interact with the U3 snoRNA or form a complex with IGF-II mRNA-binding protein 4 and M phase phosphoprotein 10. The encoded protein can bind to the 5' UTR of the insulin-like growth factor II leader 3 mRNA and may repress translation of insulin-like growth factor II during late development. The encoded protein contains several KH domains, which are important in RNA binding and are known to be involved in RNA synthesis and metabolism. A pseudogene exists on chromosome 7, and there are putative pseudogenes on other chromosomes. biological process: RNA processing, embryogenesis and morphogenesis, protein biosynthesis
**SELENBP1**: selenium binding protein 1; This gene product belongs to the selenium-binding protein family. Selenium is an essential nutrient that exhibits potent anticarcinogenic properties, and deficiency of selenium may cause certain neurologic diseases. It has been proposed that the effects of selenium in preventing cancer and neurologic diseases may be mediated by selenium-binding proteins. The exact function of this gene is not known.
**Hs.76888 (INA)**: internexin neuronal intermediate filament protein, alpha neurofilament-66, tax-binding protein
**Hs.1569 (LHX2)**: LIM/homeodomain transcription factor 2; biological process: oncogenesis
**AREG**: Amphiregulin; member of the epidermal growth factor family; autocrine growth factor as well as a mitogen for astrocytes, Schwann cells, and fibroblasts; related to EGF and TGF-alpha. Interacts with the EGF/TGF-alpha receptor to promote the growth of normal epithelial cells and inhibits the growth of certain aggressive carcinoma cell lines.
**EREG**: Epiregulin: epidermal growth factor family; ligand of EGFR and of most members of the ERBB (v-erb-b2 oncogene homolog) family of tyrosine-kinase receptors; may promote cell proliferation
**Hs.92137**: Highly similar to **L-myc-1** proto-oncogene protein.
**PLAUR**: plasminogen activator, urokinase receptor
**IMAGE:502518 (LAMB2.b)**: laminin beta 2; laminins implicated in cell adhesion, differentiation, migration, signaling, neurite outgrowth and metastasis
**KIFC3**: Kinesin family member C3; microtubule-associated motor proteins
**Hs.236361 (RNPC1)**: RNA-binding region (RNP1, RRM) containing 1
**Hs.334370 (BEX1)**: brain expressed, X-linked 1; molecular function: signal transducer activity, transcription factor activity; nucleus
**IMAGE:241530 (EPHA2)**: ephrin receptor EphA2; This gene belongs to the ephrin receptor subfamily of the protein-tyrosine kinase family. EPH and EPH-related receptors have been implicated in mediating developmental events, particularly in the nervous system. This gene encodes a protein that binds ephrin-A ligands; differentially regulated in normal and malignant cells; Levels predict lung cancer (NSCLC) recurrence and survival; Patients with EphA2 overexpression have a poorer prognosis than those without; Eph A receptors inhibit tumor angiogenesis and progression in vivo; Blockade of EphA2 activation inhibits vascular endothelial growth factor-induced angiogenesis; negative regulation by Cbl; c-Cbl-dependent EphA2 protein degradation is induced by ligand binding; estrogen and Myc negatively regulate EphA2 expression in mammary epithelial cells; EphA2 receptor tyrosine kinase is a substrate for low molecular weight tyrosine phosphatase and has a role in neoplastic transformation progression; Recent studies have demonstrated that the EphA2 receptor tyrosine kinase is frequently overexpressed and functionally altered in aggressive tumor cells, and that these changes promote metastatic character; tyrosine phosphorylated EphA2 interacts with the PTB and SH2 domains of SHC, the interaction of EphA2 with GRB2 is mediated by SHC and that this complex is necessary for EphA2-mediated activation of ERK kinases
**Fn14**: tumor necrosis factor receptor superfamily, member 12a; Fn14 contributes to nerve regeneration via a Rac1 GTPase-dependent mechanism; The cytoplasmic tail of this protein binds tumour-necrosis-factor-receptor-associated factors 1, 2, 3 and 5 and mediates nuclear factor-kappaB activation; molecular function: receptor activity, biological process: cell adhesion, apoptosis, angiogenesis, substrate-bound cell migration, cell attachment to substrate; cellular component: integral to membrane
**Hs.172199 (ADCY7)**: adenylate cyclase 7; Adenylate cyclase is a membrane bound enzyme that catalyses the formation of cyclic AMP from ATP. The adenylyl cyclase enzyme family is characterized by the presence of 12 membrane-spanning domains in its sequences; biological process: intracellular signaling cascade; cellular component: integral to plasma membrane; molecular function: magnesium ion binding
**FHOS**: formin homology 2 domain containing 1; This gene encodes a protein which is a member of the Formin/Diaphanous family of proteins. The gene is ubiquitously expressed but is found in abundance in the spleen. The encoded protein has sequence homology to Diaphanous and Formin proteins within the Formin Homology (FH)1 and FH2 domains. It also contains a coiled-coil domain, a collagen-like domain, two nuclear localization signals, and several potential PKC and PKA phosphorylation sites. It is a predominantly cytoplasmic protein and is expressed in a variety of human cell lines. The function of this protein has not been known. molecular function: actin binding
**FOXG1B**: forkhead box G1B; his gene belongs to the forkhead family of transcription factors which is characterized by a distinct forkhead domain. The specific function of this gene has not yet been determined; however, it may play a role in the development of the brain and telencephalon.
**ISL1**: ISL1 transcription factor, LIM/homeodomain, (islet-1); ISL1 encodes islet 1, a transcription factor containing two amino-terminal LIM domains and one carboxy-terminal homeodomain. ISL1 plays an important role in the embryogenesis of pancreatic islets of Langerhans. In addition, mouse embryos made deficient in ISL1 fail to undergo neural tube motor neuron differentiation.