



cGMP-mediated signaling



S. Figure 1C: ClueGO Biological Process network map. Nodes are colored based on ontology and node size indicates signi icance (all P values < 0.05).

negative regulation of synaptic transmission sensory perception of taste smooth muscle cell differentiation epithelial cell morphogenesis extracellular matrix assembly alkaline phosphatase activity regulation of superoxide metabolic process cytokine receptor activity		11 12 13 14 15 16 17	7 18 19 20 21 22 23 24 25	\$ 26 27 28 29 <b>4</b>	30 31 32 33 34 35 36 37 38	3 39 40 41 42 43 44 45 46 47 48 49 50 51 52
regulation of neuron migration acetyl-CoA metabolic process response to zinc ion regulation of myotube differentiation response to progesterone peptidyl-tyrosine dephosphorylation protein tyrosine phosphatase activity regulation of protein binding negative regulation of protein binding	3 3 3 3 6 6 6 12 7 6					
sarcomere organization N-acylphosphatidylethanolamine metabolic process phosphatidylethanolamine metabolic process calcineurin-mediated signaling calcineurin-NFAT signaling cascade cell adhesion mediator activity cell-cell adhesion mediator activity negative regulation of epithelial cell apoptotic process regulation of endothelial cell apoptotic process aromatic amino acid family metabolic process		3			3.	
potassium ion transport potassium ion transmembrane transporter activity phosphatase inhibitor activity protein phosphatase inhibitor activity cyclic-nucleotide-mediated signaling cGMP-mediated signaling adenylate cyclase-activating G protein-coupled receptor signaling pathway response to fatty acid nitric oxide mediated signal transduction long-chain fatty acid transport spinal cord development	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$					
cell differentiation in spinal cord regulation of digestive system process cellular response to retinoic acid cellular response to vitamin maternal process involved in female pregnancy regulation of stem cell proliferation neuroblast proliferation neuron recognition axonal fasciculation neuron projection fasciculation ruffle organization		4 4				
ruffle assembly regulation of ruffle assembly positive regulation of cold-induced thermogenesis response to amyloid-beta cellular response to amyloid-beta neuropeptide signaling pathway G protein-coupled peptide receptor activity neuropeptide receptor activity body morphogenesis regulation of receptor binding branching involved in blood vessel morphogenesis		6				
cellular response to UV cellular response to vitamin D sensory organ morphogenesis embryonic digestive tract development ear morphogenesis metanephros morphogenesis prostate gland development odontogenesis prostate gland morphogenesis odontogenesis of dentin-containing tooth negative regulation of developmental growth	6 3 13 3 6 3 6 3 4 10 3 6 3 6 3 4 10 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 3 6 8					
aminoglycan catabolic process negative regulation of wound healing glycosaminoglycan catabolic process response to mechanical stimulus cellular response to mechanical stimulus negative regulation of DNA biosynthetic process carboxypeptidase activity morphogenesis of a branching structure body morphogenesis_1 morphogenesis of a branching epithelium branching morphogenesis of an epithelial tube branching involved in blood vessel morphogenesis_1						
positive regulation of epidermis development positive regulation of epidermal cell differentiation positive regulation of epidermal cell differentiation positive regulation of keratinocyte differentiation regulation of keratinocyte differentiation myeloid leukocyte cytokine production mast cell mediated immunity positive regulation of interleukin-6 production positive regulation of tumor necrosis factor superfamily cytokine production molting cycle process		3				
hair cycle hair cycle process hair follicle development skin epidermis development stem cell division regulation of bone remodeling positive regulation of myeloid leukocyte differentiation granulocyte differentiation positive regulation of osteoclast differentiation stem cell division_1 somatic stem cell division regulation of stem cell proliferation_1	6 5 5 5 3 5 3 3 5 3 5 3 3 3 3 3 3 3 3 3					
neuroblast proliferation_1 hippocampus development positive regulation of release of sequestered calcium ion into cytosol positive regulation of ion transport positive regulation of cell junction assembly positive regulation of lipid transport positive regulation of calcium ion transport into cytosol detoxification detoxification of inorganic compound response to hydroperoxide xenobiotic transport		3				
xenobiotic detoxification by transmembrane export across the plasma membrane endoderm development positive regulation of embryonic development formation of primary germ layer regulation of gastrulation endoderm formation endodermal cell differentiation adult locomotory behavior walking behavior anion homeostasis	5 3 7 3 5 4 5 3 3 3 4		3			
monovalent inorganic anion homeostasis chloride ion homeostasis SMAD protein signal transduction activin receptor signaling pathway regulation of activin receptor signaling pathway pathway-restricted SMAD protein phosphorylation regulation of pathway-restricted SMAD protein phosphorylation positive regulation of pathway-restricted SMAD protein phosphorylation transepithelial transport neurotransmitter transmembrane transporter activity organic cation transport	3 5 3 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5	5				
ammonium transport bicarbonate transport ammonium transmembrane transport ammonium transmembrane transporter activity regulation of postsynaptic membrane neurotransmitter receptor levels receptor localization to synapse vesicle-mediated transport in synapse protein localization to postsynaptic membrane retrograde transport, endosome to plasma membrane receptor signaling complex adaptor activity neurotransmitter receptor transport bone remodeling						
female pregnancy maternal process involved in female pregnancy_1 response to estradiol acid secretion fatty acid derivative transport icosanoid transport prostaglandin transport response to nicotine catecholamine secretion dopamine transport regulation of catecholamine secretion	1       4         4       9         9       8         5       5         5       5         4       5         5       5         4       5         3       4         4         4         4         4         4	4				
dopamine secretion regulation of dopamine secretion synaptic transmission, cholinergic acetylcholine receptor activity pancreas development placenta development embryonic placenta development mesenchyme morphogenesis cell differentiation involved in embryonic placenta development cornification	3 3 4 3 5 10 6 3 3 5 3 5					
labyrinthine layer development labyrinthine layer morphogenesis regulation of neurotransmitter transport positive regulation of blood pressure vesicle-mediated transport in synapse_1 regulation of synaptic vesicle cycle dopamine transport_1 dopamine secretion_1 regulation of dopamine secretion_1 neurotransmitter receptor transport_1 regulation of synaptic vesicle exocytosis	7       3         11       8         3       3         3       3         3       3         5       5	4				
cell-cell adhesion via plasma-membrane adhesion molecules synapse assembly regulation of synapse assembly regulation of presynapse organization positive regulation of synapse assembly presynapse assembly regulation of presynapse assembly	10 8 6	5	7			

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detoxification_1 adult locomotory behavior_1 bone remodeling_2 detoxification of inorganic compound_1 regulation of action potential_1 positive regulation of lipid localization																						
action potential_1 temperature homeostasis_1 xenobiotic transport_1 transepithelial transport_1																						
transport across blood-brain barrier xenobiotic detoxification by transmembrane export across the plasma membrane_1 response to estradiol_2 positive regulation of ion transport_1																						
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response to mercury ior acid secretion_3 regulation of amine transport_2 negative regulation of amine transport_2 thyroid hormone transpor																						
fatty acid derivative transport_1 xenobiotic transport across blood-brain barrier xenobiotic transmembrane transporter activity regulation of anion transpor positive regulation of cold-induced thermogenesis																						
positive regulation of anion transport_1 regulation of acute inflammatory response nitric-oxide synthase activity_3 regulation of nitric-oxide synthase activity_3 anion homeostasis																						
response to dexamethasone positive regulation of acute inflammatory response cellular response to corticosteroid stimulus ammonium transmembrane transport_2																						
regulation of amino acid transport_1 regulation of amino acid transport_1 monovalent inorganic anion homeostasis_1 cellular response to dexamethasone stimulus icosanoid transport_1																						
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cellular response to glucocorticoid stimulus positive regulation of fatty acid transpor acidic amino acid transpor positive regulation of myeloid leukocyte differentiation_1																						
prostaglandin transport_1 long-chain fatty acid transport_1 chloride ion homeostasis_1 positive regulation of calcium ion transport into cytosol_1 dicarboxylic acid transmembrane transporter activity																						
positive regulation of osteoclast differentiation_2 cell communication by electrical coupling actin filament-based movement_1 bone remodeling_3 endocrine process																						
production of molecular mediator involved in inflammatory response_1 regulation of action potential_2 action potential_2 temperature homeostasis_2 regulation of tube size																						
intestinal absorption_2 membrane depolarization actin-mediated cell contraction_1 regulation of membrane depolarization_1 regulation of cell communication by electrical coupling																						
regulation of endocrine process regulation of cardiac muscle cell action potentia regulation of actin filament-based movemen positive regulation of blood circulation_1 regulation of endothelial cell proliferation_1																						
striated muscle contraction regulation of tube diamete negative regulation of blood pressure_3 regulation of amine transport_3 negative regulation of amine transport 3																						
cardiac muscle cell action potential_1 membrane repolarization membrane depolarization during action potentia positive regulation of tumor necrosis factor superfamily cytokine production_2 regulation of the force of heart contraction																						
renal system process involved in regulation of systemic arterial blood pressure regulation of muscle contraction_1 regulation of membrane repolarization cell communication involved in cardiac conduction regulation of blood vessel diamete																						
positive regulation of cold-induced thermogenesis_4 endocrine hormone secretion cell-cell signaling involved in cardiac conduction nitric-oxide synthase activity_4																						
gap junction assembly positive regulation of tumor necrosis factor production_2 negative regulation of hormone secretion_1 regulation of nitric-oxide synthase activity_4																						
cardiac muscle contraction positive regulation of lipase activity_1 muscle tissue morphogenesis cardiac muscle cell contraction_1 cardiac muscle cell membrane repolarization																						
cardiac atrium developmen cardiac ventricle developmen regulation of heart rate by cardiac conductior atrial septum developmen cardiac atrium morphogenesis																						
regulation of smooth muscle contraction_1 regulation of striated muscle contractior cell communication by electrical coupling involved in cardiac conductior atrial cardiac muscle cell to AV node cell communication AV node cell to bundle of His cell communication																						
Purkinje myocyte to ventricular cardiac muscle cell communication SA node cell to atrial cardiac muscle cell communication negative regulation of blood vessel diameter_1 cellular response to amyloid-beta_1 gonadotropin secretion																						
SA node cell to atrial cardiac muscle cell signaling atrial cardiac muscle cell to AV node cell signaling AV node cell to bundle of His cell signaling Purkinje myocyte to ventricular cardiac muscle cell signaling positive regulation of phospholipase activity_																						
regulation of vasoconstriction_2 regulation of gonadotropin secretion_1 positive regulation of vasoconstriction_1 cardiac muscle tissue morphogenesis regulation of cardiac muscle contraction																						
cardiac muscle cell action potential involved in contraction regulation of cardiac muscle cell contraction negative regulation of peptide hormone secretion_1 ventricular cardiac muscle cell membrane repolarization regulation of phospholipase C activity																						
vasoconstriction_1 ventricular cardiac muscle tissue morphogenesis follicle-stimulating hormone secretion SA node cell action potentia AV node cell action potentia																						
positive regulation of phospholipase C activity_1 ventricular cardiac muscle cell action potentia atrial cardiac muscle cell action potentia positive regulation of peptidyl-tyrosine phosphorylation_1																			3			

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S. Figure 1E: ClueGO Biological Process ontologies, percent representation: Colors represent ontology groups.



S. Figure 2A: ClueGO Cellular Component network map. Nodes are colored based on ontology and node size indicates significance (all P values < 0.05).





S. Figure 2: B) ClueGO Cellular Component ontologies: Number and percent genes per ontology C) Percent representation: Colors represent ontology groups.

anchored component of membrane 3.85% \*\*

anchored component of plasma membrane 3.85% .

voltage-gated potassium channel complex 3.85% .



S. Figure 3A: ClueGO Molecular Function network map. Nodes are colored based on ontology and node size indicates significance (all P values < 0.05).

# crGART to HeLa molecular function %genes per term



### alkaline phosphatase activity PDZ domain binding receptor serine/threonine kinase binding nitric-oxide synthase binding cell-cell adhesion mediator activity regulation of receptor binding protein tyrosine phosphatase activity cytokine receptor activity carboxypeptidase activity neurotransmitter transmembrane transporter activity ammonium transmembrane transporter activity acetylcholine receptor binding acetylcholine receptor activity regulation of protein binding negative regulation of protein binding proteoglycan binding nitric-oxide synthase activity regulation of nitric-oxide synthase activity potassium ion transmembrane transporter activity voltage-gated potassium channel activity phosphatase inhibitor activity protein phosphatase inhibitor activity beta-catenin binding receptor signaling complex adaptor activity xenobiotic transmembrane transporter activity dicarboxylic acid transmembrane transporter activity ATPase-coupled xenobiotic transmembrane transporter activity carbon-oxygen lyase activity hydro-lyase activity carbonate dehydratase activity peptide receptor activity peptide hormone binding G protein-coupled peptide receptor activity neuropeptide receptor activity phospholipase A2 activity (consuming 1,2-dipalmitoylphosphatidylcholine) phospholipase A2 activity consuming 1,2-dioleoylphosphatidylethanolamine) phospholipase A2 activity phospholipase A1 activity phosphatidylserine 1-acylhydrolase activity 1-acyl-2-lysophosphatidylserine acylhydrolase activity positive regulation of lipase activity regulation of phospholipase activity phospholipase C activity

positive regulation of phospholipase activity positive regulation of lipid kinase activity regulation of phosphatidylinositol 3-kinase activity regulation of phospholipase C activity positive regulation of phospholipase C activity

# crGART to HeLa molecular function terms per group



S. Figure 3: B) Molecular Function ontologies: Number and percent genes per ontology C) Percent representation: Colors represent ontology groups.

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alkaline phosphatase activity 1.85% \*\* carboxypeptidase activity 1.85% receptor serine/threonine kinase binding 1.85% nitric-oxide synthase binding 1.85% cell-cell adhesion mediator activity 1.85% regulation of receptor binding 1.85% protein tyrosine phosphatase activity 1.85% cytokine receptor activity 1.85% neurotransmitter transmembrane transporter activity 3.7% \*\* acetylcholine receptor binding 3.7% regulation of protein binding 3.7% \* nitric-oxide synthase activity 3.7% potassium ion transmembrane transporter activity 3.7% phosphatase inhibitor activity 3.7%



S. Figure 4A: ClueGO Reactome Pathways network map. Nodes are colored based on pathway and node size indicates significance (all P values < 0.05).

### crGART to HeLa Reactome pathways %genes per term



crGART to HeLa Reactome pathways terms per group



S. Figure 4: B) Reactome Pathways: Number and percent genes per pathway C) Percent representation: Colors represent pathway groups.

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Class B/2 (Secretin family receptors) 3.45% .

Post-translational modification: synthesis of GPI-anchored proteins 3.45% \*\*

Cell surface interactions at the vascular wall 3.45%  $^{\star\star}$ 

Diseases associated with O-glycosylation of proteins 3.45%.

Transport of inorganic cations/anions and amino acids/oligopeptides 3.45% .



Α

S. Figure 5A: ClueGO Reactome Reactions network map. Nodes are colored based on reaction and node size indicates significance (all P values < 0.05).

### crGART to HeLa Reactome reactions %genes per term







### S. Figure 5: B) Reactome Reactions: Number and percent genes per reaction C) Percent representation: Colors represent reaction groups.

### В

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HRASLS transfer acyl group from PC to PE to form NAPE 4.17% \*\*

- PSGs bind proteoglycans and TGF-beta1 4.17% \*\*
- GPLD1 hydrolyses GPI-anchors from proteins 4.17% \*\*
- Exocytosis of specific granule membrane proteins 4.17%

PI3K inhibitors block PI3K catalytic activity 8.33%

Liganded Gs-activating GPCR acts as a GEF for Gs 8.33%

SCNAs:SNCBs transport Na+ from extracellular region to cytosol 8.33% \*

Liganded Gq/11-activating GPCRs act as GEFs for Gq/11 12.5% \*



### crGART to HeLa biological process %genes per term



В



S. Figure 6: B) ClueGO Biological Process ontologies: Number and percent genes per ontology C) Percent representation: Colors represent ontology groups.