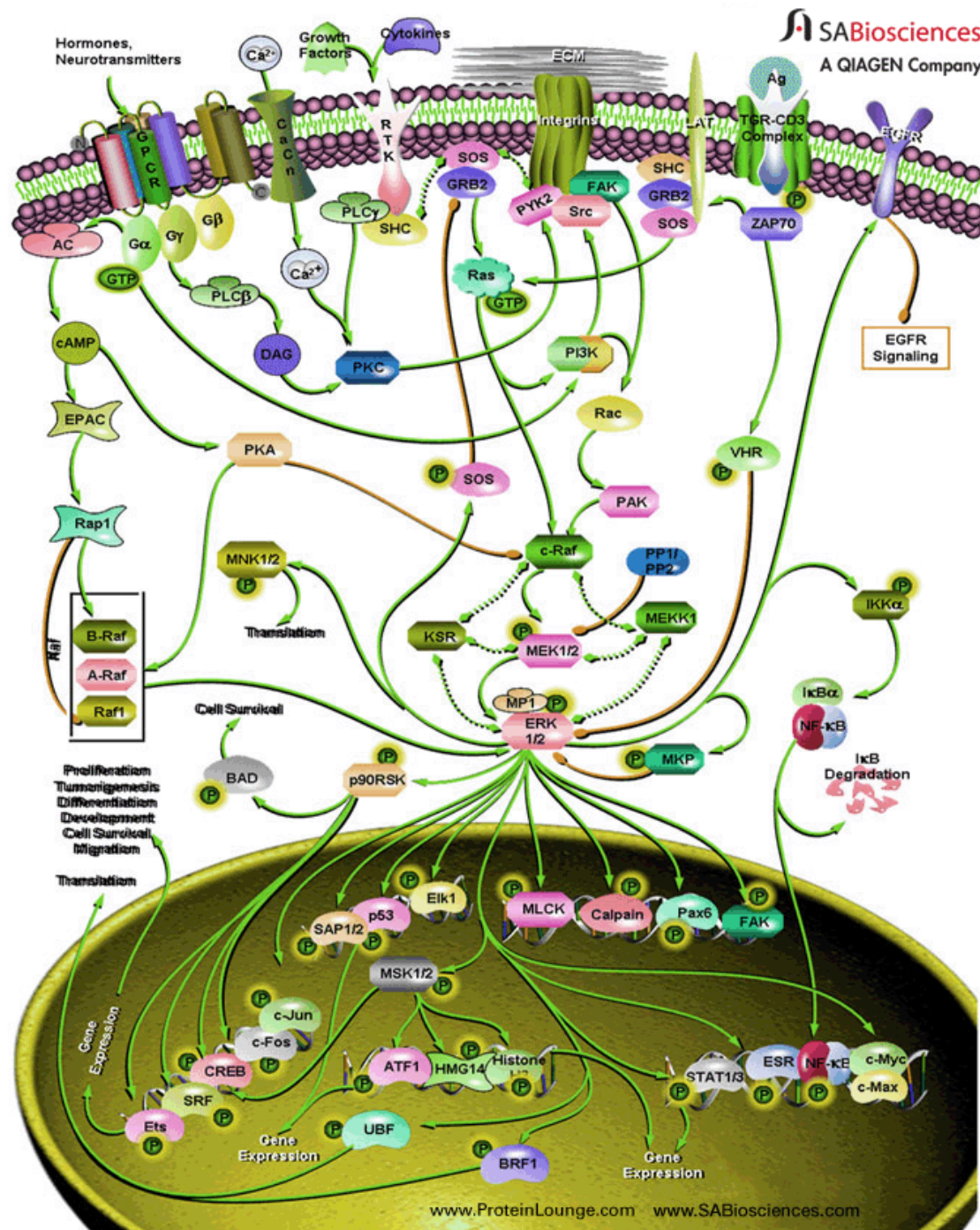


Signaling in GO

Rebecca Foulger c/o Signaling Working Group

GO Consortium Meeting, Bar Harbor
September 2010



Background

- The signaling working group previously revised the top level signaling terms to give:

signaling ; GO:0023052

--%behavioral signaling ; GO:0023032

--%cell-cell signaling ; GO:0007267

--%signaling pathway ; GO:0023033

----%cell surface receptor linked signaling pathway ; GO:0007166

-----%Notch signaling pathway ; GO:0007219

--<signaling process ; GO:0023046

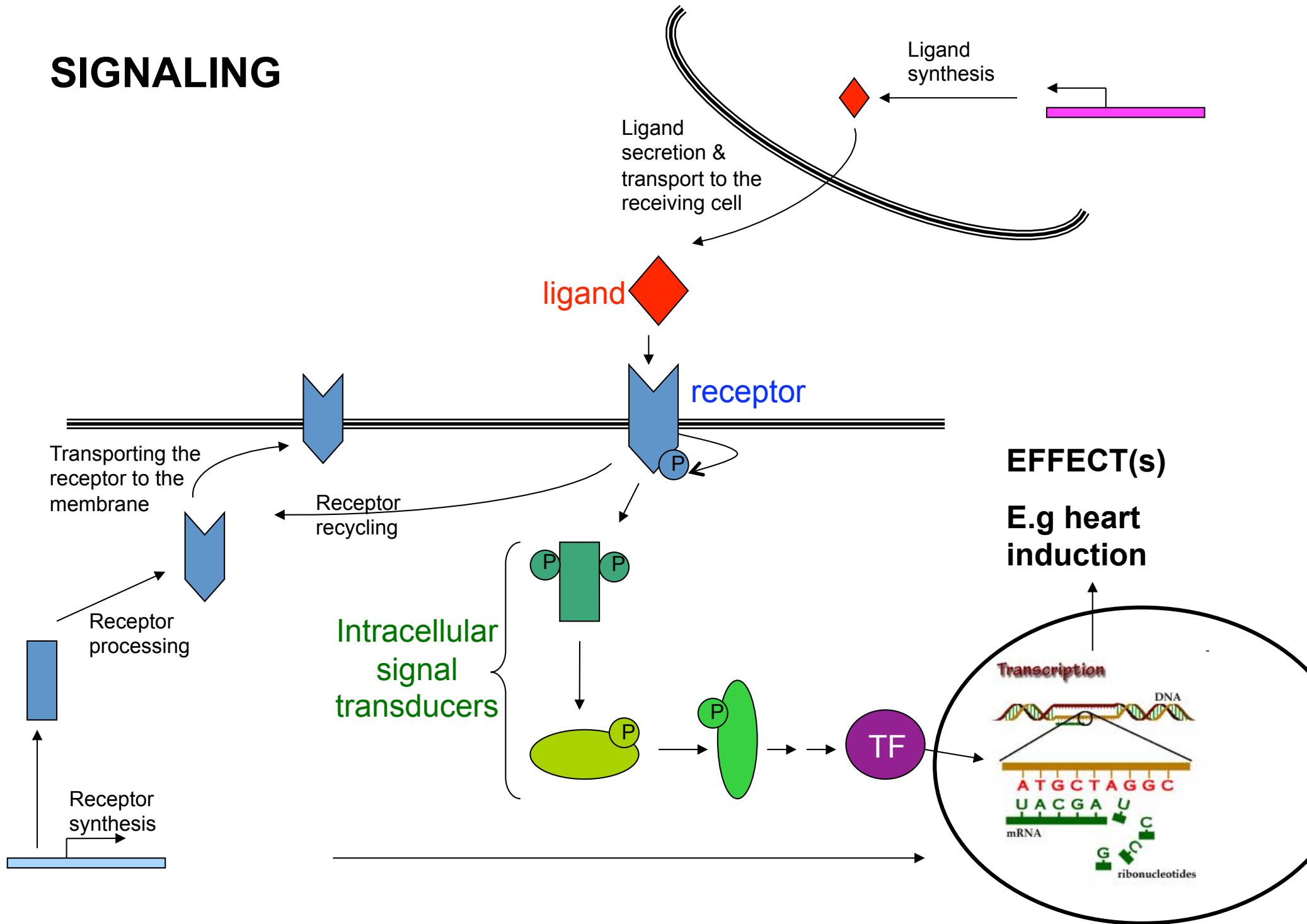
----%signal transmission ; GO:0023060

-----%signal transduction ; GO:0007165

-----%receptor recycling ; GO:0001881

- **GO:002xxxx terms were created by the signaling group in the overhall
- As a result 'signal transduction ; GO:0007165' is no longer the top level signaling term.

SIGNALING



Defining the beginning and end of a signaling pathway

- Existing definitions:

signaling pathway ; GO:0023033

The series of molecular events whereby information is sent from one location to another within a living organism or between living organisms.

Notch signaling pathway ; GO:0007219

The series of molecular signals initiated by binding of an extracellular ligand to a Notch receptor on the surface of the target cell.

- The SG discussed whether the pathway should be expanded to include upstream events E.g.

transport of the receptor to the cell surface

transport of the ligand to the receiving cell

synthesis of the ligand/processing of the receptor

... And the consensus was **NO***

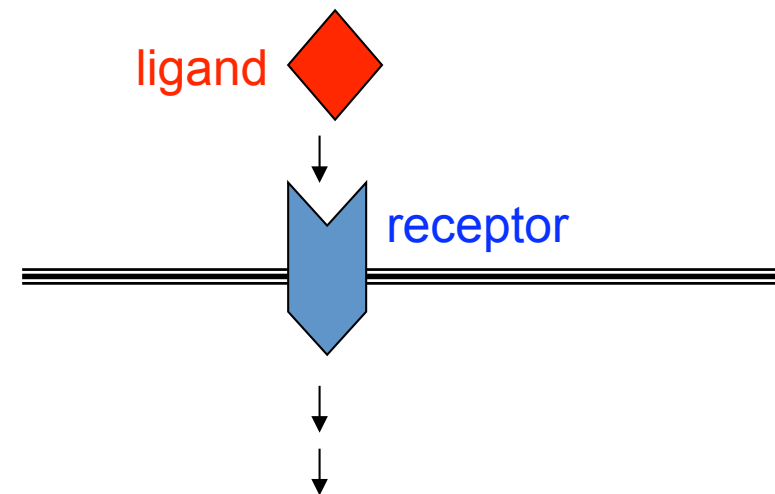
(*these should be annotated to '**regulation** of x pathway')

BMP signaling pathway

chemokine-mediated signaling pathway

sugar mediated signaling pathway

(far-red light signaling pathway)



Notch signaling pathway

Roundabout signaling pathway

Wnt receptor signaling pathway

dopamine receptor signaling pathway

The start & end of a signaling pathway

- Not every signaling pathway starts with receptor-ligand binding (E.g. light-induced signaling pathways).
- We decided the pathway does begin with reception of the signal though, so the following update to the definition of 'signaling pathway ; GO:0023033' is proposed:

Old:

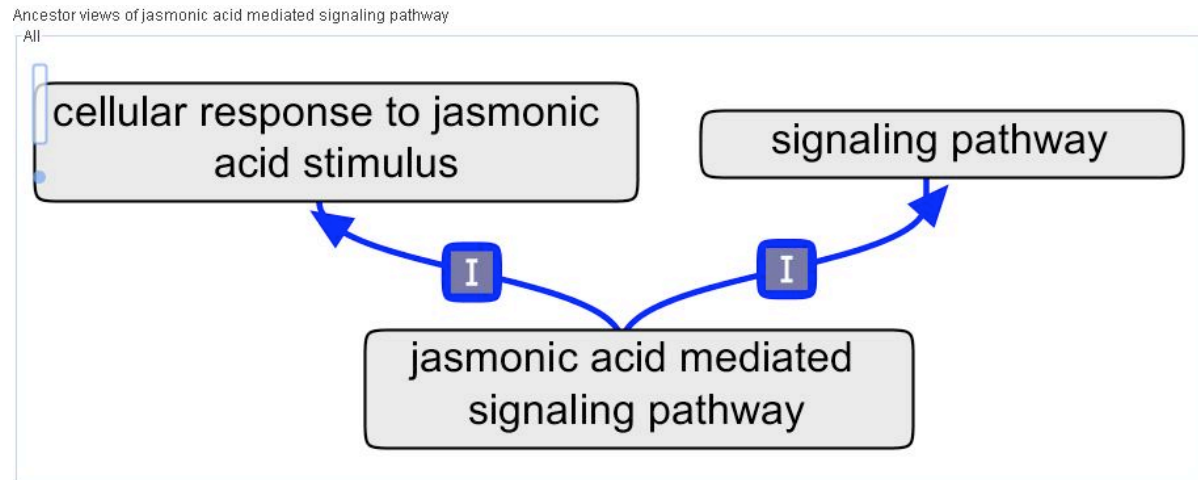
The series of molecular events whereby information is sent from one location to another within a living organism or between living organisms.

Proposed New:

The series of molecular events whereby a signal is received, transmitted and interpreted. A signaling pathway begins with reception of the signal, for example binding of a ligand to a receptor or activation of a receptor via a conformational change, and ends when a response has been triggered.

Signaling and Response

- Currently many signaling terms are children of response terms:



- Response is considered broader than the signaling (signaling is an example of a response).
- Works well for ligand-defined but not receptor-defined pathways.
E.g. epidermal growth factor receptor signaling pathway ; GO:0007173
Def: The series of molecular signals generated as a consequence of an epidermal growth factor receptor binding to one of its physiological ligands.

Therefore GO:0007173 can't have 'cellular response to epidermal growth factor stimulus ; GO:0071364' as a parent.

Signaling and Cell Communication

cell communication ; GO:0007154

Any process that mediates interactions between a cell and its surroundings.

Encompasses interactions such as signaling or attachment between one cell and another cell, between a cell and an extracellular matrix, or between a cell and any other aspect of its environment.

•Old:

signaling ; GO:0023052

--%cell communication ; GO:0007154

----%cellular response to extracellular stimulus ; GO:0031668

•To fix:

cell communication ; GO:0007154

--%cell-cell signaling ; GO:0007267

--%cellular response to extracellular stimulus ; GO:0031668

Intracellular signaling

- There were a number of separate intracellular terms:

intracellular signaling pathway ; GO:0023034

intracellular signaling cascade ; GO:0007242

signal transmission via intracellular cascade ; GO:0023013

intracellular receptor mediated signaling pathway ; GO:0030522

- A number of cell-surface receptor signaling terms were incorrectly under intracellular signaling, so these links were removed:

glutamate signaling pathway ; GO:0007215

immune response-regulating cell surface receptor signaling pathway ; GO:0002768

integrin-mediated signaling pathway ; GO:0007229

lipopolysaccharide-mediated signaling pathway ; GO:0031663

osmosensory signaling pathway ; GO:0007231

pattern recognition receptor signaling pathway ; GO:0002221

toll-like receptor signaling pathway ; GO:0002224

smoothed signaling pathway ; GO:0007224

Toll signaling pathway ; GO:0008063

Wnt receptor signaling pathway ; GO:0016055

Intracellular signaling (cont)

- The current tree stands at:

```
signaling pathway ; GO:0023033
--%intracellular signaling pathway ; GO:0023034
----%intracellular receptor mediated signaling pathway ; GO:0030522
----%intracellular signal transduction ; GO:0035556
```

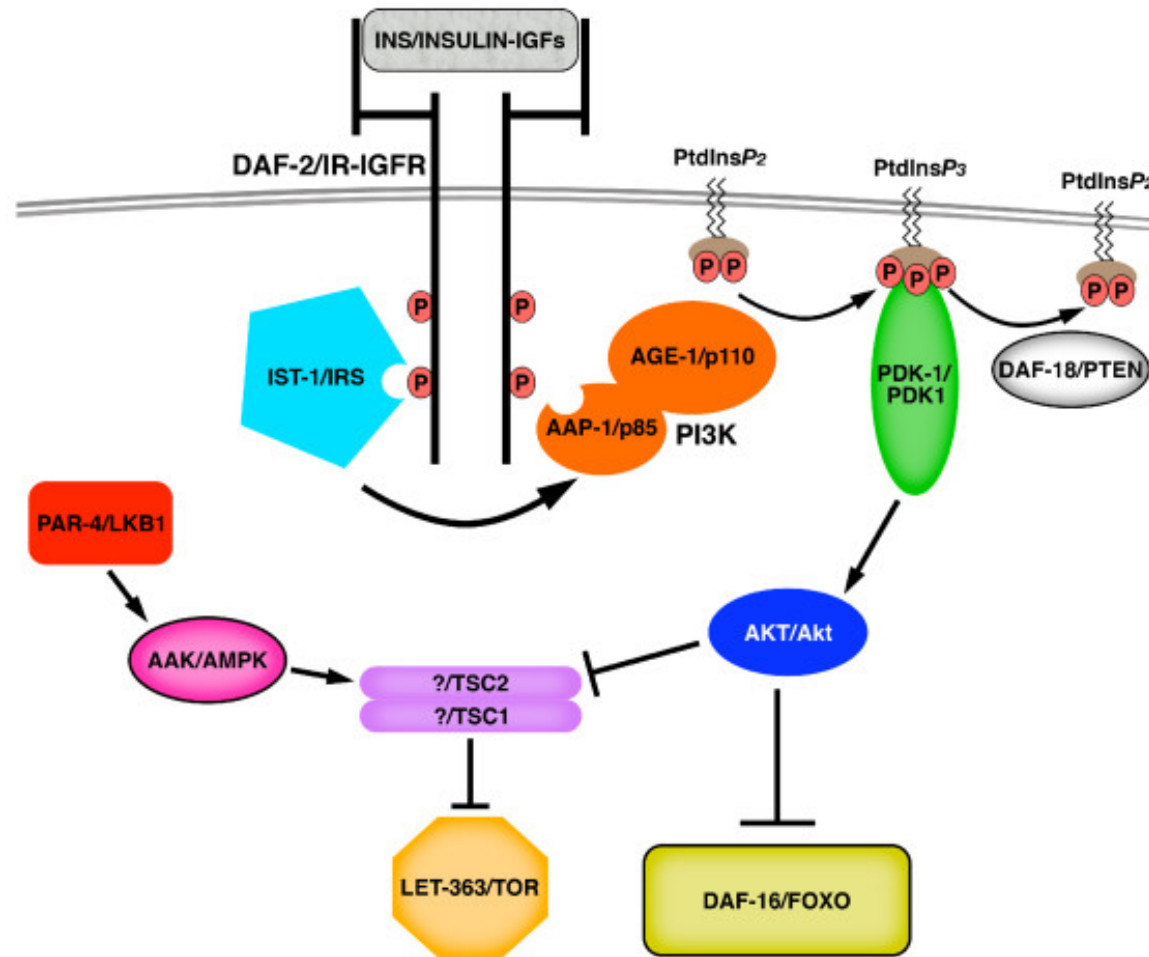
- There is a proposal to obsolete intracellular signaling pathway ; GO:0023034 to give:

```
signaling pathway ; GO:0023033
--<intracellular signal transduction ; GO:0035556
----%hippo signaling cascade ; GO:0035329
----%phosphoinositide 3-kinase cascade ; GO:0014065
```

- To distinguish between complete pathways (from ligand down) to bits of pathways (cassettes), we use the term 'cascade'.

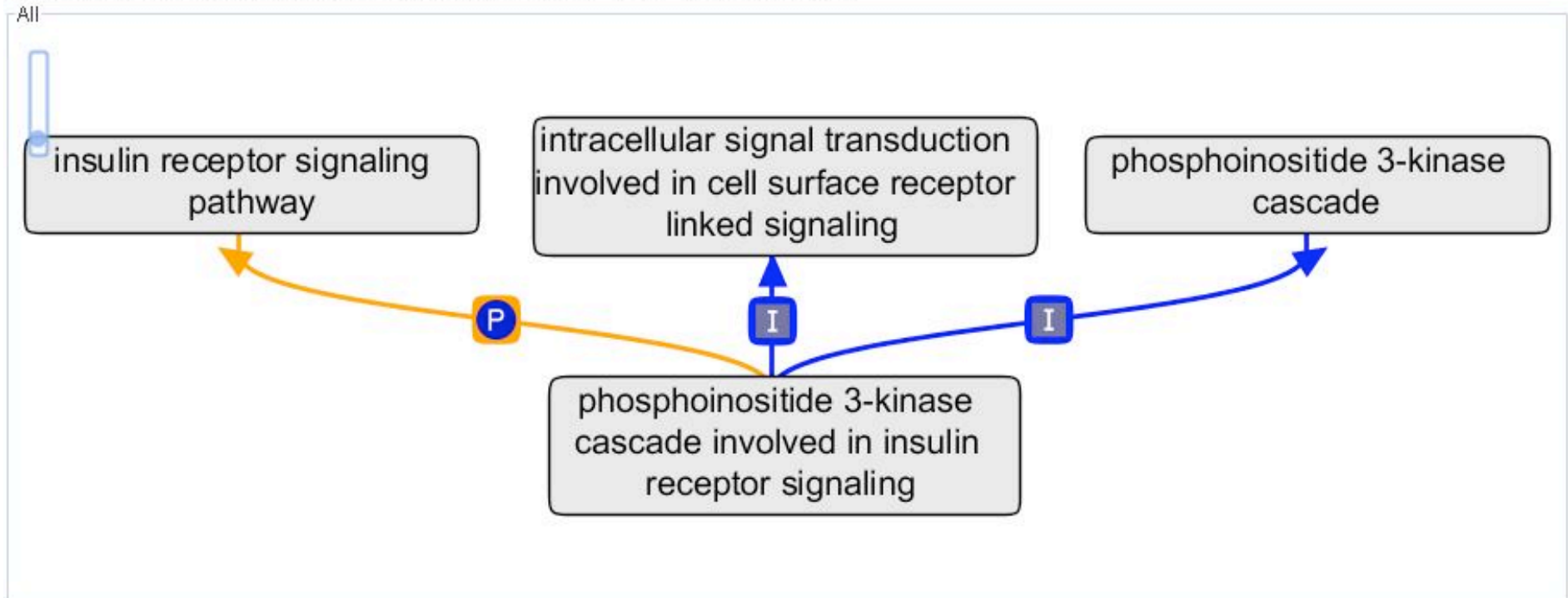
(intracellular signal transduction ; GO:0035556 has the exact synonym: intracellular signaling cascade)

Linking receptors and downstream cassettes/cascades



Linking receptors and downstream cassettes/cascades

Ancestor views of phosphoinositide 3-kinase cascade involved in insulin receptor signaling



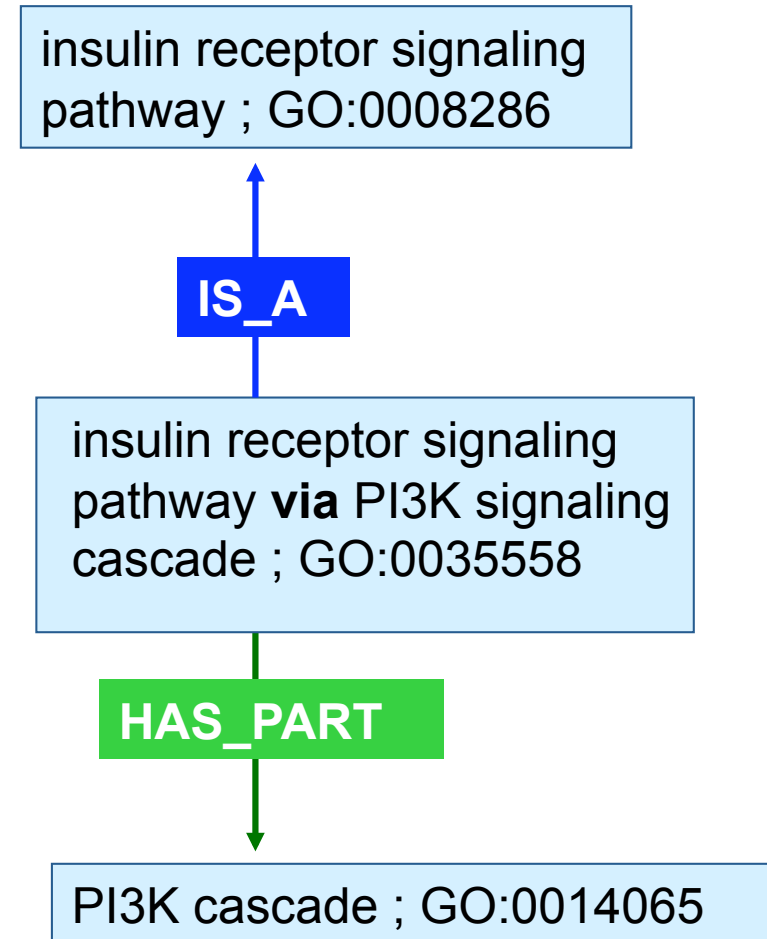
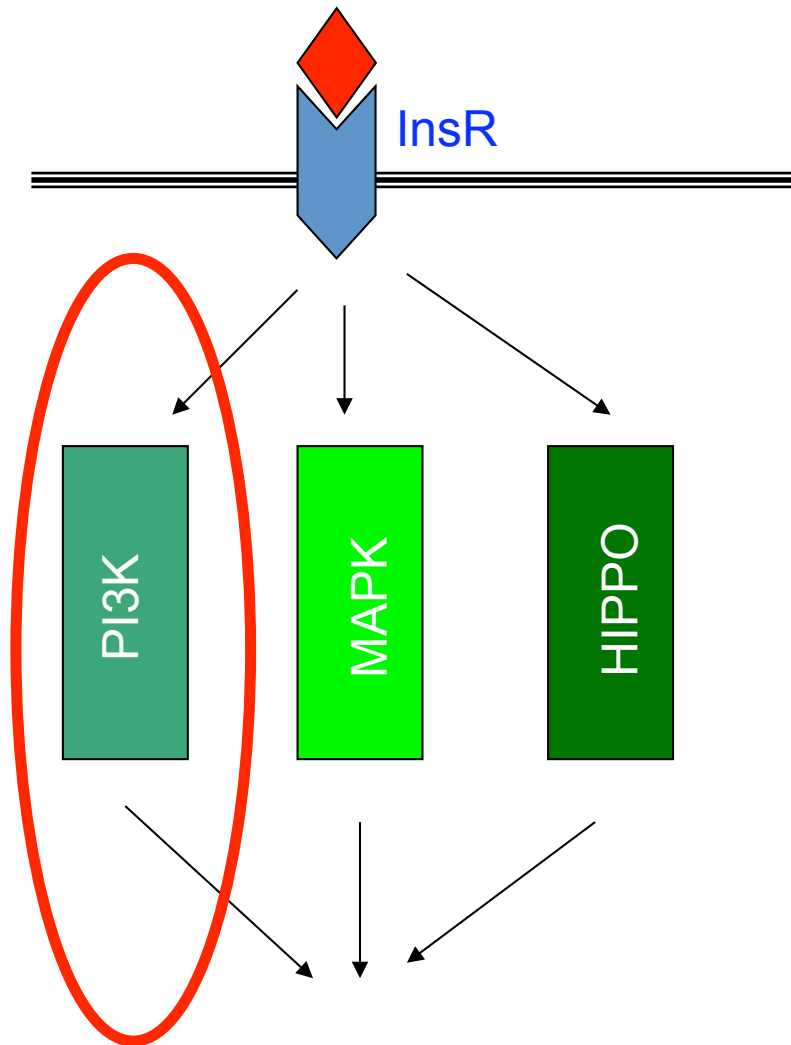
- After talking with David, Jane and co, we need to change the wording of these:

'by'

'through'

'via'

'downstream of'



Wnts

- In combination with the RefGenome group, we split Wnt signaling into canonical and non-canonical nodes:

Wnt receptor signaling pathway ; GO:0016055

--%canonical Wnt receptor signaling pathway ; GO:0060070

--%non-canonical Wnt receptor signaling pathway ; GO:0035567

- canonical Wnt receptor signaling pathway ; GO:0060070

Exact synonym: Wnt receptor signaling pathway through beta-catenin

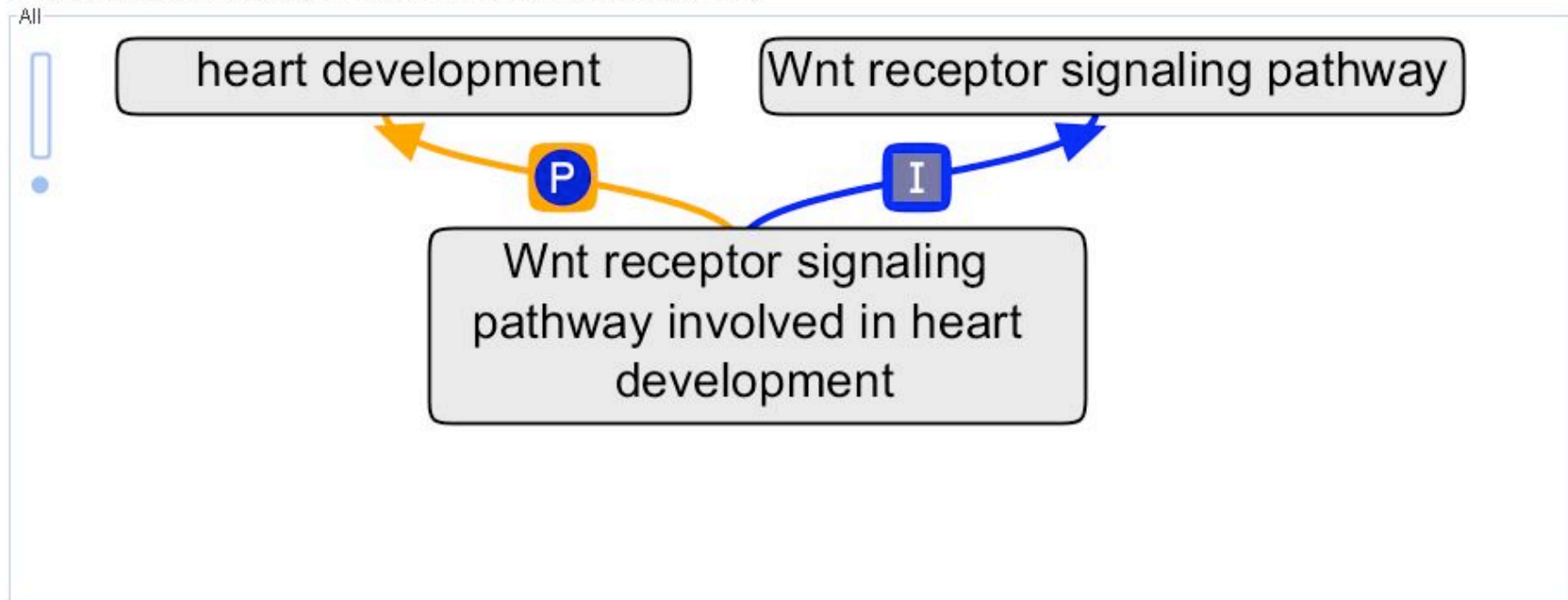
- non-canonical Wnt receptor signaling pathway ; GO:0035567

Exact synonym: beta-catenin-independent Wnt receptor signaling pathway

Signaling pathways and downstream effects

- Wnt receptor signaling pathway **involved in** heart development ; GO:0003306
- canonical Wnt receptor signaling pathway **involved in** positive regulation of wound healing ; GO:0044330
- epidermal growth factor receptor signaling pathway **involved in** lung development ; GO:0060507

Ancestor views of Wnt receptor signaling pathway involved in heart development



RECEPTOR LIGAND

- BHF have requested that we bring back the term 'ligand' (SF: 3056631) to distinguish all the other proteins that bind to receptors from the signal protein that binds to a receptor to activate it.

- Midori pointed out that the following terms already exist:

receptor agonist activity ; GO:0048018 (1 annotation)

receptor antagonist activity ; GO:0048019 (38 annotations)

receptor agonist activity ; GO:0048018

Interacts with receptors such that the proportion of receptors in the active form is increased.

- Currently working through whether to:

Add synonym 'receptor ligand' to these terms

Add a parent 'receptor ligand activity' **

cytokine and morphogen

- Alex and Ruth have been working to better define:

cytokine activity ; GO:0005125

morphogen activity ; GO:0016015

SF:3056635

RECEPTOR

- Current definition is: E.g. epidermal growth factor receptor activity ; GO:0005006
Combining with an epidermal growth factor to initiate a change in cell activity.

BUT.... the EGFR has a number of functions:

1. Binding to EGF
2. A kinase for itself
3. A kinase for downstream targets
4. Signal transducer

- The EGF-binding function is independent of the kinase activity, but with the current hierarchy, the whole term is under 'kinase activity':

protein tyrosine kinase activity ; GO:0004713

--%transmembrane receptor protein tyrosine kinase activity; GO:0004714

----%epidermal growth factor receptor activity ; GO:0005006

RECEPTOR

- Use HAS_PART relationships ?

signal transducer activity

--%receptor activity

----%EGF receptor activity ; GO:0005006

-----HAS_PART: tyrosine kinase activity

-----HAS_PART: EGF binding

OTHER TASKS TO TACKLE

- Receptor definitions aren't always consistent with the pathways:

epidermal growth factor receptor activity ; GO:0005006

Combining with an epidermal growth factor to initiate a change in cell activity.

epidermal growth factor receptor signaling pathway ; GO:0007173

The series of molecular signals generated as a consequence of an epidermal growth factor receptor binding to one of its physiological ligands.

activin receptor signaling pathway ; GO:0032924

A series of molecular signals generated as a consequence of any member of the activin family binding to a cell surface receptor.

OTHER TASKS TO TACKLE

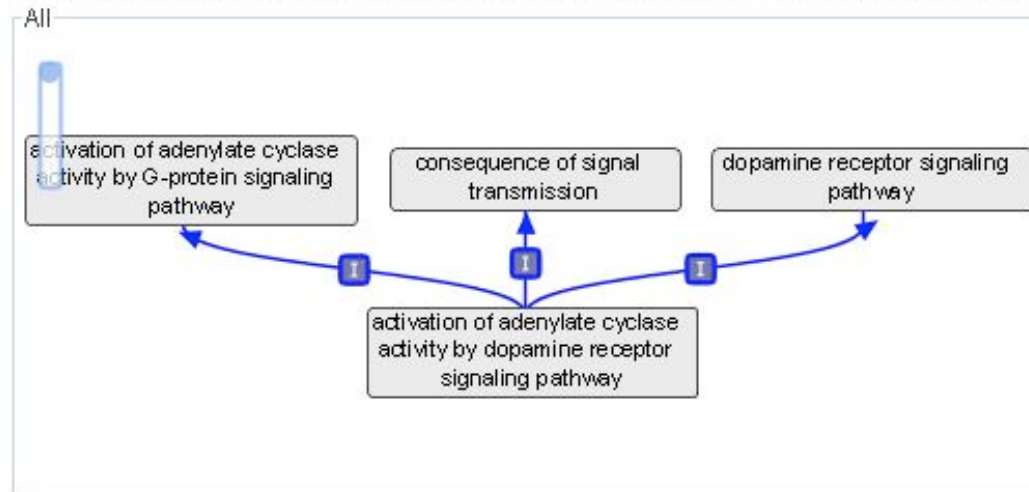
signaling process ; GO:0023046

--%**consequence of signal transmission ; GO:0023050**

----%regulation of gene expression as a consequence of signal transmission ; GO:0023019


-----%activation of adenylate cyclase activity by dopamine receptor signaling pathway ; GO:0007191

Ancestor views of activation of adenylate cyclase activity by dopamine receptor signaling pa...



- Use involved in?

OTHER TASKS TO TACKLE

- ▣ all : all [447044 gene products]
- ▣ ⓘ GO:0003674 : molecular_function [365944 gene products]
- ▣ ⓘ GO:0060089 : molecular transducer activity [21198 gene products]
- ▣ ⓘ GO:0004871 : signal transducer activity [21198 gene products]
- ▣ ⓘ **GO:0005057 : receptor signaling protein activity [917 gene products]** 
- ▣ ⓘ GO:0005062 : hematopoietin/interferon-class (D200-domain) cytokine receptor signal transducer activity [11 gene products]
- ▣ ⓘ GO:0030545 : receptor regulator activity [177 gene products]
- ▣ ⓘ GO:0004702 : receptor signaling protein serine/threonine kinase activity [492 gene products]
- ▣ ⓘ GO:0005076 : receptor signaling protein serine/threonine kinase signaling protein activity [0 gene products]
- ▣ ⓘ GO:0009400 : receptor signaling protein serine/threonine phosphatase activity [1 gene product]
- ▣ ⓘ GO:0005081 : receptor signaling protein serine/threonine phosphatase signaling protein activity [0 gene products]
- ▣ ⓘ GO:0004716 : receptor signaling protein tyrosine kinase activity [65 gene products]
- ▣ ⓘ GO:0008268 : receptor signaling protein tyrosine kinase signaling protein activity [6 gene products]
- ▣ ⓘ GO:0004728 : receptor signaling protein tyrosine phosphatase activity [9 gene products]
- ▣ ⓘ GO:0005082 : receptor signaling protein tyrosine phosphatase signaling protein activity [2 gene products]
- ▣ ⓘ GO:0005071 : transmembrane receptor protein serine/threonine kinase signaling protein activity [27 gene products]
- ▣ ⓘ GO:0005066 : transmembrane receptor protein tyrosine kinase signaling protein activity [34 gene products]

Actions...
Last action: Opened
GO:0005057
[Graphical View](#)
[Permalink](#)
[Download...](#)
[OBO](#)
[RDF/XML](#)
[GraphViz dot](#)

- Define or obsolete
- Go right back to 'signal transducer activity ; GO:0004871'

All changes/meeting minutes are documented at:

<http://gocwiki.geneontology.org/index.php/Signaling>