SUMMARY OF GO SIGNALING WORKSHOP

February 16th and 17th 2011

EBI

http://gocwiki.geneontology.org/index.php/Signaling_Workshop_February_2011

Attendees

- GO *Annotators*
  - Ruth Lovering (BHF-UCL)
  - Varsha Khodiyar (BHF-UCL)
  - Sandra Orchard (Intact)
  - Peter D'Eustachio (Reactome)
  - Rachael Huntley (GOA)
  - Val Wood (Pombase)
  - Susan Tweedie (FlyBase)
  - Alex Diehl (remote attendee)

- GO *Editors*
  - Midori Harris
  - Rebecca Foulger (Wednesday)
  - Paola Roncaglia

- GO *Experts*
  - Andrea Townsend-Nicholson (UCL)
  - Andrew Chatr-aryamontri (BioGRID)

- GO *Developers*
  - Chris Mungall (Thursday)

Topics Discussed

- Defining the start and end points of all signaling processes
  - signaling
  - generation of a signal
  - signal transduction
    - initiation of signal transduction
    - termination of signal transduction
  - signaling pathway
  - signaling cascade
  - paracrine/autocrine/endocrine signaling

- Connecting cell-surface receptors with the intracellular signaling cassettes

- Dealing with non 1:1 ligand:receptor combinations

- How does receptor-mediated endocytosis fit with signaling?

- Receptors: transport vs signaling

How it looks now...

signaling ; GO:0023052

- For molecular signaling, we need to define a clearer start point.
- Synthesis of the signal and the receptor (transcription, translation, processing) should not be part of signaling. These processes REGULATE signal transduction.
- Signaling should begin with an active signal.
- We need to work through examples to test this.

- *In some cases, the stimulus is the signal (eg nutrient signaling pathway).*
- *In some cases, the signal is synthesised in response to the stimulus.*
- *In some cases, the signal is released in response to the stimulus (eg insulin)*

Old Def: The entirety of a process whereby information is transmitted. This process begins with the initiation of the signal and ends when a response has been triggered.

New Def: The entirety of a process in which information is transmitted. This process begins with an active signal and ends when a response has been triggered.

Glossary:

Signal: *any variable property or parameter that serves to convey information, and may be a physical entity such as a gene product or small molecule, a photon, or a change in state such as movement or voltage change.*

endocrine vs paracrine

- After consultations with endocrinologists (Thanks Stan!), and signaling meeting, we will add the following terms in:

- Comments of the terms will advise using with caution.

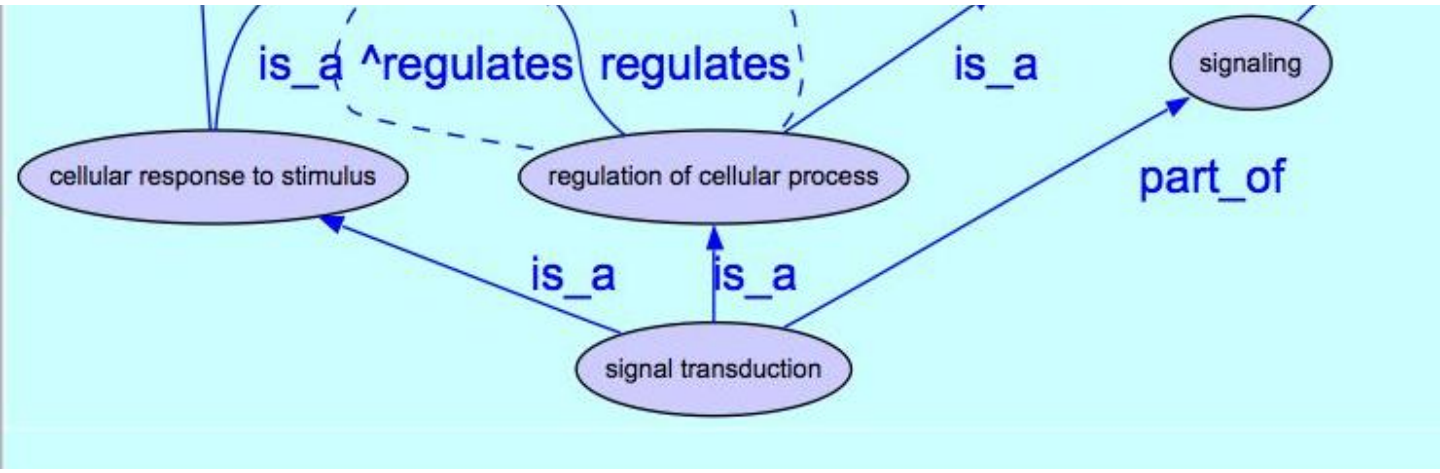
endocrine signaling ; GO:NEW
Def: The transfer of information from one cell to another, where an endocrine hormone is transported from the signal-producing cell to the receiving cell via the circulatory system (via blood, lymph or cerebrospinal fluid). The signaling cell and the receiving cell are often distant to each other.
is_a: cell-cell signaling ; GO:0007267
part_of: endocrine process ; GO:0050886
part_of: multicellular organismal signaling ; GO:0035637
ISBN:3527303782, ISBN:0199264678

paracrine signaling ; GO:NEW
Def: The transfer of information from one cell to another, where the signal travels from the signal-producing cell to the receiving cell by passive diffusion or bulk flow in intercellular fluid. The signaling cell and the receiving cell are usually in the vicinity of each other.
ISBN:3527303782
is_a: cell-cell signaling ; GO:0007267
('paracrine signaling' is currently a narrow synonym of cell-cell signaling ; GO:0007267)

signal transduction; GO:0007165

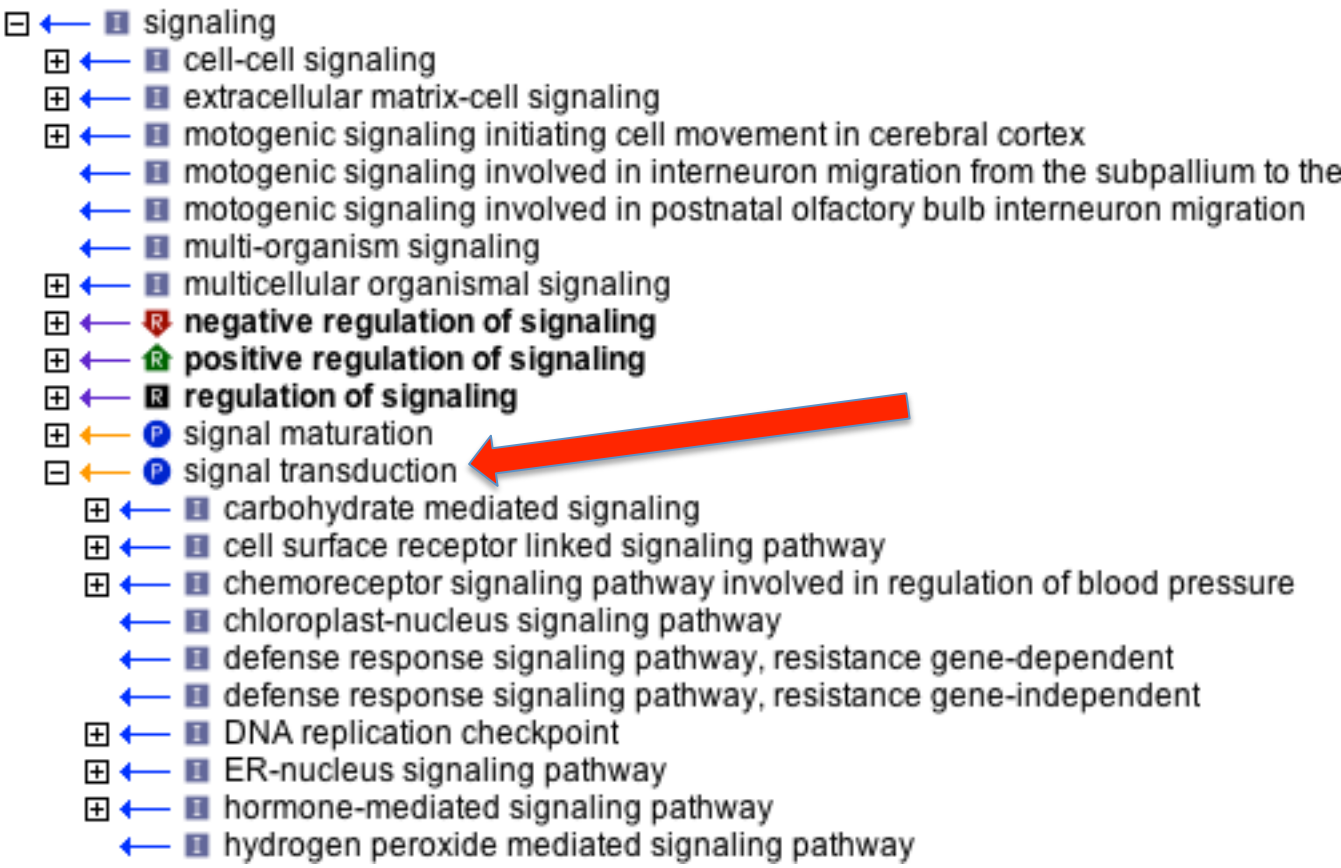
Revised Def: The cellular process in which a signal is conveyed to trigger a change in the activity or state of a cell. Signal transduction begins with reception of a signal, e.g. a ligand binding to a receptor or receptor activation by a stimulus such as light, and ends with regulation of a downstream cellular process, e.g. regulation of transcription or regulation of a metabolic process. Signal transduction covers signaling from receptors located on the surface of the cell, and signaling via molecules located within the cell. For signaling between cells, signal transduction is restricted to events at and within the receiving cell.

- **Begins with** reception of a signal (E.g. receptor-ligand binding)
- **Ends with** regulation of a downstream process (eg regulation of transcription, direct regulation of apoptosis, regulation of glycogen synthesis etc.
- **Limited to** molecular events in the receiving cell.



signal transduction; GO:0007165

- **Pathways are children of 'signal transduction'.**



- The ligand is part of the pathway.
  - Therefore the ligand can be annotated to 'signal transduction'
  - Therefore, the ligand can be annotated to 'response to x'. E.g. insulin can be annotated to 'response to insulin'.
  - A ligand is NOT a signal transducer.

PATHWAYS

- There are 2 'stages' of downstream processes:
  - CELLULAR (E.g. transcription, protein synthesis, apoptosis)
  - MULTI-CELLULAR (E.g. heart development, wound healing, pattern formation)

- Each pathway REGULATES a **CELLULAR PROCESS**.

- And these cellular processes are involved in multi-cellular processes (E.g. heart development, pattern formation, lung induction).

- So the GO term:
  - **Wnt receptor signaling pathway involved in kidney development ; GO:0061289**

    means Wnt receptor signaling pathway involved in regulating x cellular process (probably transcription) that contributes to kidney development.

- Transcription factors **ARE** part of a pathway because they pass the signal on to RNA polymerase. They are the last GP in the pathway.

- Glycogen synthase is **NOT** part of the pathway because it is not passing the signal on… it is part of the downstream cellular process of glycogen synthesis.

initiation of signal transduction; GO:0023036

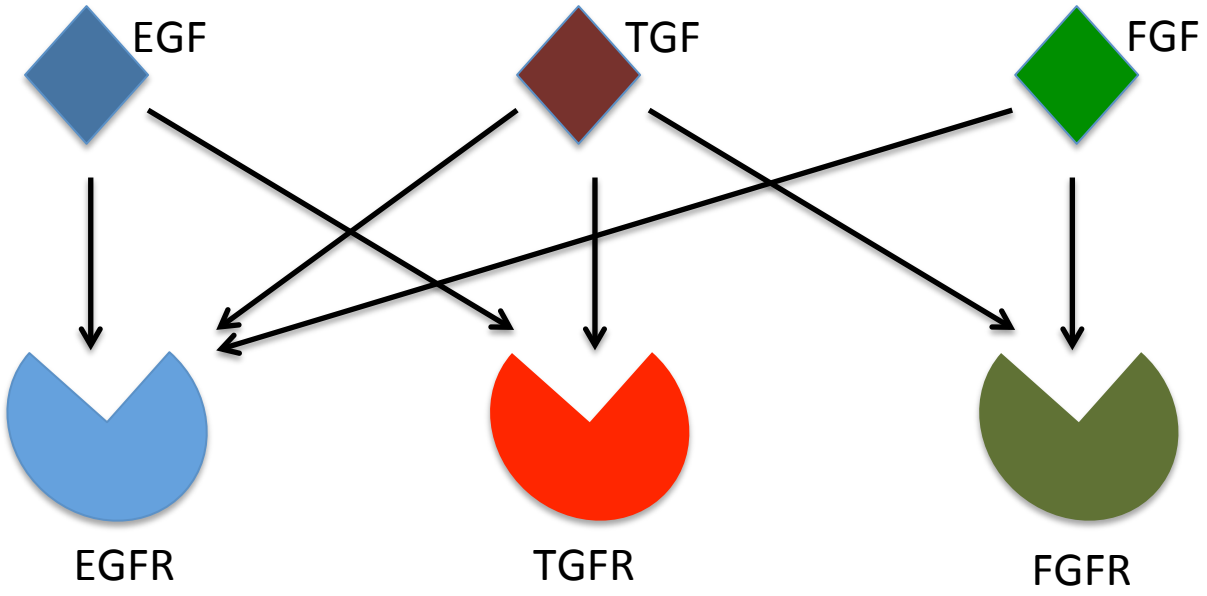
termination of signal transduction ; GO:0023021

- The definitions of these terms don't match the comments.
- It's unclear which GPs should be annotated to these terms.
- The end of 'initiation of signal transduction' was unclear.
- Termination of signal transduction should be covered by 'negative regulation of signal transduction ; GO:0009968'.
- Termination of signal transduction has 0 annotations.

PROPOSAL:

- Therefore, these terms will be proposed for **obsoletion**. The addition of process-function links between E.g. 'receptor activity', 'receptor agonist activity' and 'signal transduction' will fill the gaps.

non 1:1 receptor:ligand binding

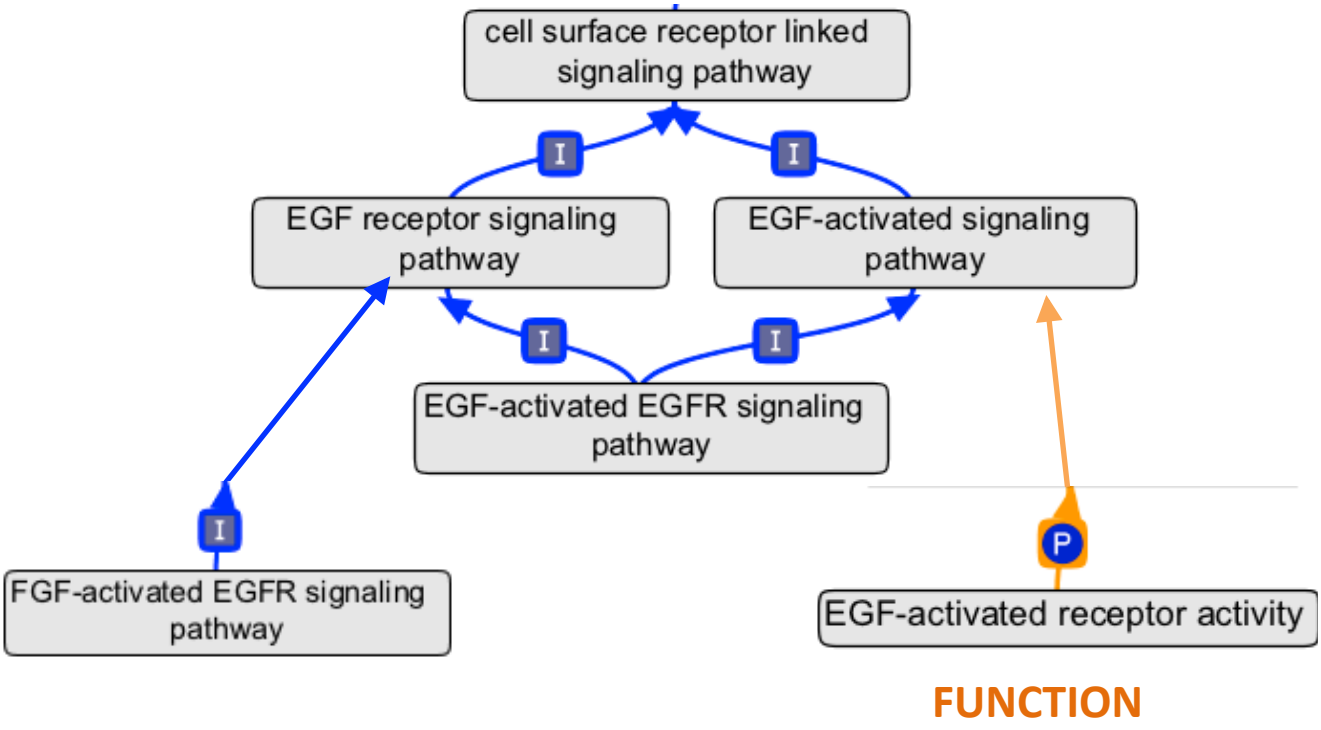


- Need to capture that ligands can bind > 1 receptor.
- Need to capture that receptors can bind > 1 ligand.

PROBLEMS

- Receptors are often named after the first ligand they are found to bind
- In function, we have to annotate the activity and not the gene product.
  - *To have the function of an EGFR, it has to bind EGF (and transduce the signal by a phosphorylation step). If it transmits the signal that is PDGF, it has the activity of a PDGFR (regardless of what the biologist calls it).*

Proposal:



To distinguish the activity from the name:

RENAME: epidermal growth factor receptor activity

TO: epidermal growth factor-binding receptor activity (OR)
epidermal growth factor-activated receptor activity

still to work out....

epidermal growth factor receptor binding activity ; GO:0005154

Q: is this binding to:

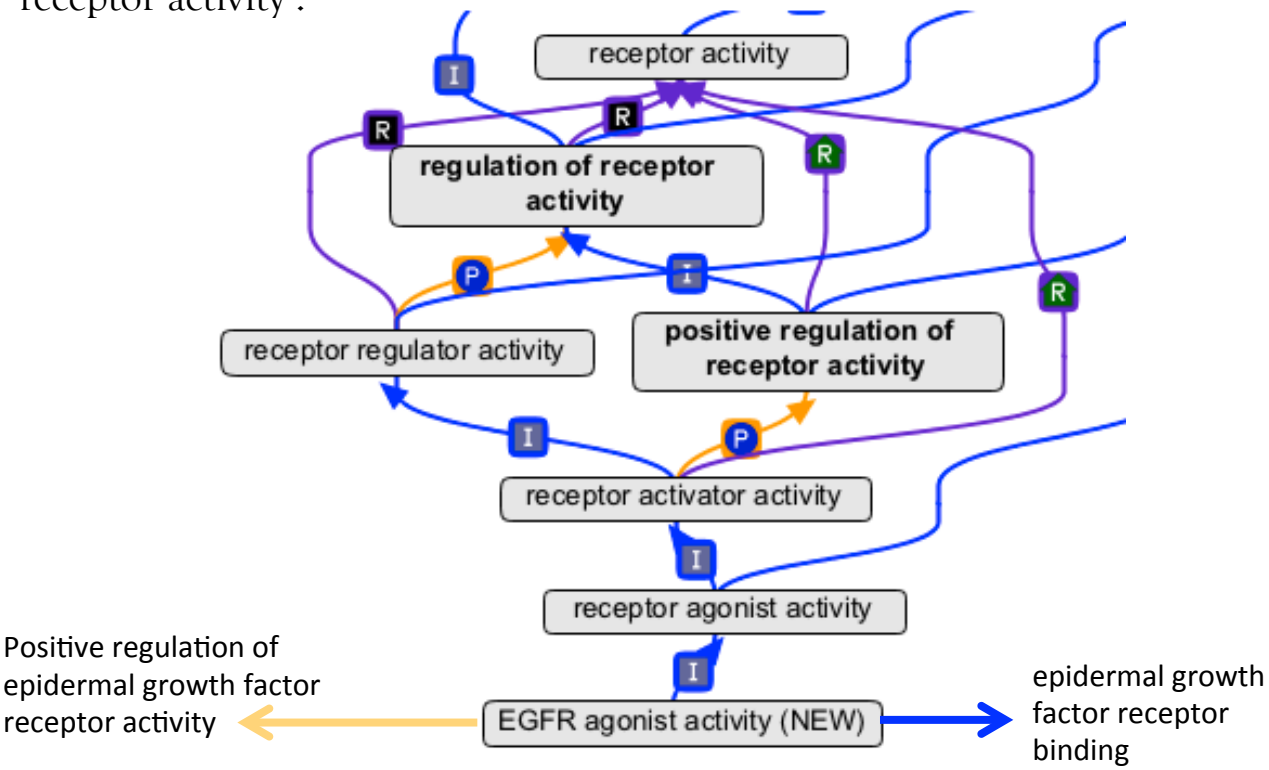
- The gene product 'EGFR'?

OR

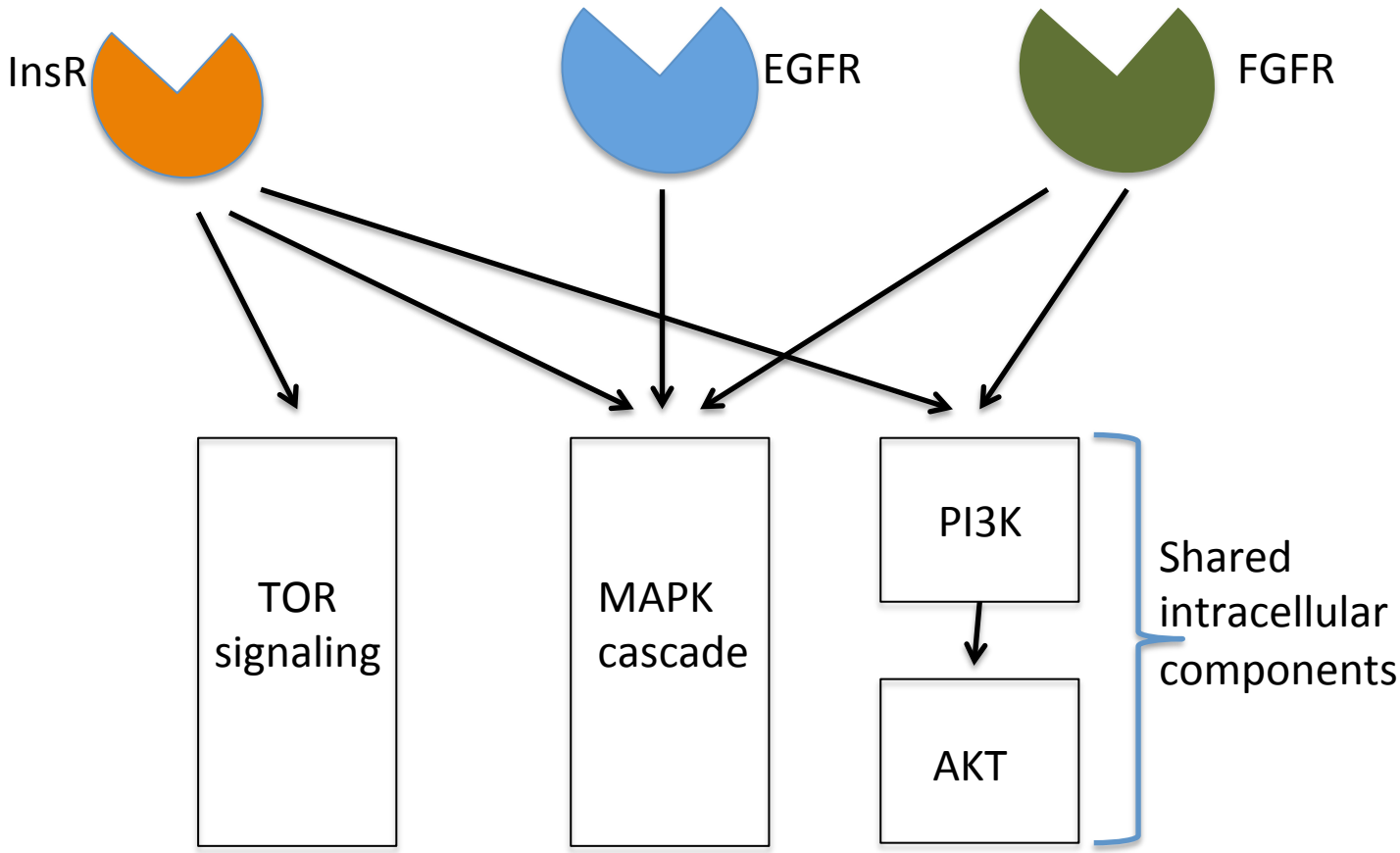
- A gene product with 'EGF-activated receptor activity'?

This is important if we start to make specific receptor-specific agonist terms. Biologically, it would make sense for a new term 'EGFR agonist activity' to mean any ligand that can activate the gene product 'EGFR'.

BUT .... it would link back to regulation of 'epidermal growth factor receptor activity'.



INTRACELLULAR CASSETTES



PROBLEM: How to connect up the intracellular cassettes with the upstream receptors

Can look at from perspective of:

perspective of receptor signaling via multiple routes.

OR

AKT being a hub to multiple upstream receptors

4 options....

- 1/ insulin receptor signaling pathway **VIA** TOR signaling cascade
- 2/ TOR signaling cascade **INVOLVED IN** insulin receptor signaling pathway
- 3/ **REGULATION** OF TOR signaling cascade by insulin receptor signaling pathway
- ~~4/ Don't connect them~~

❖ Each option would involve annotating a different subset of the pathway.

❖ Decided that '**VIA**' was the best option.
  - Need to decide whether this allows annotation of GPs upstream, within and downstream of TOR cascade.

❖ Still outstanding Qs for future conference calls.....
  - Where does each cascade begin and end?
  - Should PI3K cascade and AKT cascade terms be merged?
  - Does each cascade have to be whole? (E.g. what if a MAPKK phosphorylates a substrate that is not a MAPK?)
  - Is MAPK part of the MAPKKK cascade? (general consensus is yes, and therefore translocation to the nucleus and phosphorylation of downstream TFs is part of the cascade).
  - Is it still a protein kinase cascade if it includes non phosphorylation steps?
  - Should they be named after the first or last kinase in the cascade?
  - Should they be called 'cascades' if there's no amplification?

Options in more detail...

- 1/ insulin receptor signaling pathway **VIA** TOR signaling cascade

Insulin receptor signaling pathway
[is_a] insulin receptor signaling pathway via TOR signaling cascade
[HAS_PART] TOR signaling pathway

- 2/ TOR signaling cascade **INVOLVED IN** insulin receptor signaling pathway

Insulin receptor signaling pathway
[part_of] TOR signaling cascade involved in insulin receptor signaling pathway

TOR signaling cascade
[is_a] TOR signaling cascade involved in insulin receptor signaling pathway

- 3/ **REGULATION OF** TOR signaling cascade by insulin receptor signaling pathway

Insulin receptor signaling pathway
[is_a]regulation of TOR signaling cascade by insulin receptor signaling pathway

TOR signaling cascade
[regulates] regulation of TOR signaling cascade by insulin receptor signaling pathway
(may have to reconsider where a pathway ends)

RECEPTORS

- Q: Should receptors be split into those that signal and those that transport?
- Q: Are ion-gated ligand channels (eg P2X receptor) receptors?
- Q: How does receptor-mediated endocytosis fit with signaling?
  - Is there a signaling step in RME?

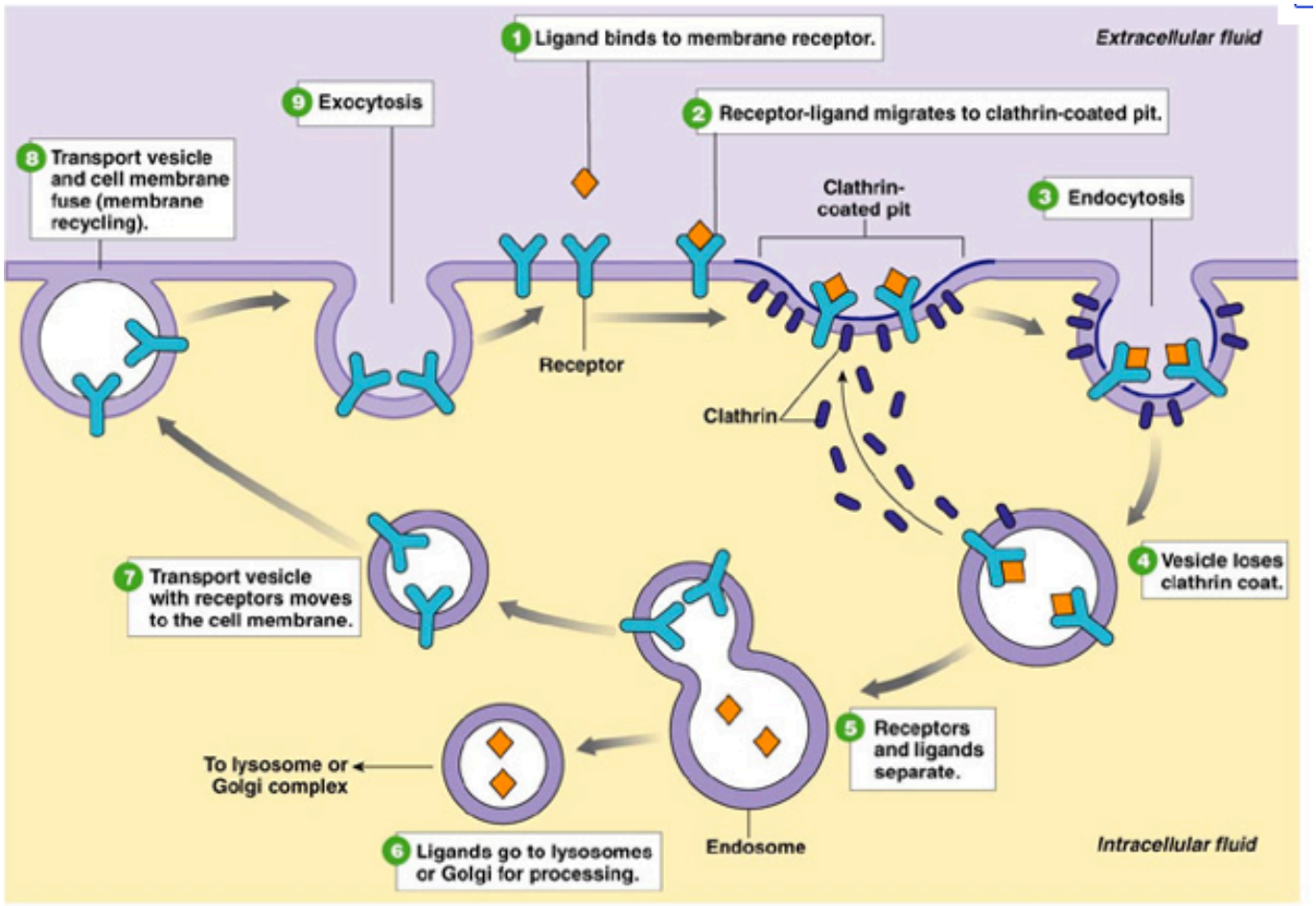


Fig. 5-24

Receptor decisions

- Rename ‘receptor activity ; GO:0004872’ to ‘signaling receptor activity’
- It should stay in function.
- Add comment: “This does not refer to receptors such as transporters, “mop-up” receptors, decoy receptors, adhesion receptors, importin receptor, nutrient receptors”, to make clear that there are other types of receptors.

ligand-dependent nuclear hormone receptor

PROBLEM:

How to join the receptor activity and the transcription factor activity of a 'nuclear' hormone receptor.

- *Current Def: A ligand-dependent receptor found in the nucleus of the cell.*
- *New Definition: Combining with a cytosolic signal and transmitting the signal from one side of the nuclear membrane to the other to regulate transcription. (Need to check that all do transfer across nuclear membrane).*
- New is_a parent: GO:0003706 ligand-regulated TF activity

Outstanding Questions:

Do we want to keep 'nucleus' in the name: it ACTS in the nucleus, but starts off in the cytoplasm.

Reactome and GO

- Chris Mungall gave a talk about making automatic Reactome-GO cross-references.
- Another reason to define start and stop points for pathways
- Reactome's start and stop points aren't always the same as GO.
  - E.g. for Notch signaling, Reactome begin with transport and processing of the Notch receptor. In GO, the Notch signaling pathway begins with receptor-ligand binding at the cell surface.
- Reactome say that they can split their pathways.
- We need to coordinate with Reactome on these.

Other Stuff

- Proposal to obsolete 'receptor signaling protein activity'
- This fits with a previous proposal (with HAS_PARTs)
- The fate of 'signal transducer activity' is undecided. With process:function links to 'signal transduction', I'd be happy to see it obsoleted.