

# eFIP (functional impact of phosphorylated proteins)

## Background on the system

eFIP (1) is a tool that is currently under development at University of Delaware but it is being used and tested by the Protein Ontology (PRO)(2) curators. It is used to find relevant papers for phosphorylated proteins that are involved in protein-protein interaction, allowing the creation of ontology terms for modified proteins and the addition of GO annotation for protein binding (e.g. [http://purl.obolibrary.org/obo/PR\\_000026167](http://purl.obolibrary.org/obo/PR_000026167)).

The input in eFIP is a gene name, and the output is a list of all relevant articles where the corresponding protein is phosphorylated. eFIP ranks papers based on information content that includes phosphorylation, protein-protein interaction (PPI) and informative terms (iTerms) for a given protein.

## Example of eFIP article list for CAV1

All articles listed are about CAV1 phosphorylation, but these are ranked by the co-occurrence of phosphorylation site mention for this protein (orange tag), PPI (green tag) and /or iTerms (informative terms). All articles with PPI tag should be considered curatable for PRO.

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### Abstracts for gene CAV1 - Caveolin 1, caveolae protein, 22kda

Other short names: cav1; cav-1; cav 1; cavi; cav-i; cav i; fc07c04; wu.fc07c04; mgc:107940; mgc-107940; mgc 107940; caveolin1; caveolin-1; caveolin 1; bsc13; bsc1-3; bsc1 3; cav; cgl3; cgl-3; cgl 3; mstp085; mstp-085; mstp 085; vip21; vip-21; vip 21; caveolin 1; mgc:187299; mgc-187299; mgc 187299

Other long names: caveolin 1, caveolae protein, 22kda; caveolin 1; caveolin-1; caveolin-i; caveolin i; testis derived transcript; othump00000025031; caveolae protein, 22-kd; caveolin 1 caveolae protein, 22kd; caveolin 1, alpha isoform; caveolin 1, beta isoform; caveolin-1 beta isoform protein; cell growth-inhibiting protein 32, cell growth-inhibiting protein-32; caveolin 1, caveolae protein; otmusp00000028492; otmusp00000028496; caveolin, caveolae protein 1; caveolin, caveolae protein-1; cav

Total abstracts mentioning CAV1 with phosphorylation: [118](#)

Rank	PMID	Species	Title	SITE	PPI	ITERM
1	PMID 18789131	human	Radiation-induced <b>caveolin-1</b> associated EGFR internalization is linked with nuclear EGFR transport and activation of DNA-PK.	●	●	●
2	PMID 15466865	human	Src-mediated tyrosine phosphorylation of <b>caveolin-1</b> induces its association with membrane type 1 matrix metalloproteinase	●	●	●
3	PMID 12921535	mice, human	Fyn is required for oxidative- and hyperosmotic-stress-induced tyrosine phosphorylation of <b>caveolin-1</b> .	●	●	●
4	PMID 11075810	mice, human	Constitutive and growth factor-regulated phosphorylation of <b>caveolin-1</b> occurs at the same site (Tyr-14) in vivo: identification of a c-Src/Cav-1/Grb7 signaling cassette.	●	●	●
5	PMID 16388599		Identification of phosphocaveolin-1 as a novel protein tyrosine phosphatase 1B substrate.	●	●	●
6	PMID 11451957		Palmitoylation of <b>caveolin-1</b> at a single site (Cys-156) controls its coupling to the c-Src tyrosine kinase: targeting of dually acylated molecules (GPI-linked, transmembrane, or cytoplasmic) to caveolae effectively uncouples c-Src and <b>caveolin-1</b> (TYR-14).	●	●	●
7	PMID 16568240	human	<b>Caveolin-1</b> interacts with the chaperone complex TCP-1 and modulates its protein folding activity.	●	●	●
8	PMID 11805080	mice	A phosphotyrosine-dependent protein interaction screen reveals a role for phosphorylation of <b>caveolin-1</b> on tyrosine 14: recruitment of C-terminal Src kinase.	●	●	●
9	PMID 17121865		RhoA activation in mesangial cells by mechanical strain depends on caveolae and <b>caveolin-1</b> interaction.	●	●	●

For each article eFIP extracts information about the phosphorylated protein and its binding partner, and presents the user the evidence for such assertion.

For example, PMID: 11075810 contains information about phosphorylation of CAV1 and its binding to Grb7. This will be considered a curatable article. The table shows the sentences that are the source for the information extracted.

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Go to PubMed **PMID 11075810 for gene CAV1 - Caveolin 1, caveolae protein, 22kda**

Other short names: cav1; cav-1; cav 1; cavi; cav-i; cav i; fc07c04; wu:fc07c04; mgc107940; mgc-107940; mgc 107940; caveolin1; caveolin-1; caveolin 1; bscl3; bscl-3; bscl 3; cav; cgl3; cgl-3; cgl 3; mstp085; mstp-085; mstp 085; vip21; vip-21; vip 21; caveolin 1; mgc187299; mgc-187299; mgc 187299

Other long names: caveolin 1, caveolae protein, 22kda; caveolin 1; caveolin-1; caveolin-i; caveolin i; testis derived transcript; otthump00000025031; caveolae protein, 22-kd; caveolin 1 caveolae protein, 22kd; caveolin 1, alpha isoform; caveolin 1, beta isoform; caveolin-1 beta isoform protein; cell growth-inhibiting protein 32; cell growth-inhibiting protein-32; caveolin 1, caveolae protein; ottmusp00000028492; ottmusp00000028496; caveolin, caveolae protein 1; caveolin, caveolae protein-1; cav

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**Species:** mice, human

Sentence	Phosphorylation			Impact to protein-protein interactions	
	Substrate	Site	Kinase	How	What
6,7	caveolin-1	---	---	---	pTyr -binding molecules
8	caveolin-1	tyrosine 14	---	confers	binding to Grb7
8,9	caveolin-1	tyrosine 14	---	demonstrate	that binding of Grb7 to tyrosine 14-PHOSphorylated caveolin-1

Below the table is the corresponding abstract, with color-tagged entities: substrate (phosphoprotein), the site, kinase and binding partners, and these can be selected/deselected.

**Toggle highlights:**  Substrate  Kinase  Phosphorylation site  Protein-protein interaction  iTerm

Title 1 Constitutive and growth factor -regulated PHOSphorylation of **caveolin-1** occurs at **the same site (Tyr-14)** in vivo : identification of a c-Src/Cav-1/Grb7 signaling cassette .

Abstract 2 Caveolin-1 was first identified as a PHOSphoprotein in Rous sarcoma virus ( RSV ) -transformed chicken embryo fibroblasts .

3 **Tyrosine 14** is now thought to be the principal site for recognition by c-Src kinase ; however , little is known about this PHOSphorylation event .

4 Here , we generated a monoclonal antibody ( mAb ) probe that recognizes only tyrosine 14-PHOSphorylated caveolin-1 .

5 Using this approach , we show that caveolin-1 (Y14) is **a specific tyrosine kinase subSTRate** that is constitutively phosphorylaTED in Src- and Abl -transformed cells and transiently PHOSphorylated in a regulated fashion during growth factor signaling .

6 We also provide evidence that tyrosine-PHOSphorylated **caveolin-1** is localized at the major sites of tyrosine kinase signaling , i.e.focal adhesions .

7 By analogy with other signaling events , we hypothesized that caveolin-1 could serve as a docking site for **pTyr -binding molecules** .

8 In support of this hypothesis , we show that PHOSphorylation of **caveolin-1** on **tyrosine 14** confers **binding to Grb7** ( an SH2-domain containing protein ) both in vitro and in vivo .

9 Furthermore , we demonstrate **that binding of Grb7 to tyrosine 14-PHOSphorylated caveolin-1** functionally augments anchorage -independent growth and epidermal growth factor ( EGF ) -stimulated cell migration .

10 We discuss the possible implications of our findings in the context of signal transduction .

By contrast, PMID:17190831 contains information only about CAV1 phosphorylation and would not be relevant for PPI curation.

Toggle highlights:	
<input checked="" type="checkbox"/>	Substrate
<input checked="" type="checkbox"/>	Kinase
<input checked="" type="checkbox"/>	Phosphorylation site
<input type="checkbox"/>	Protein-protein interaction
<input type="checkbox"/>	iTerm

  

Title	1	Caveolin-1 tyrosine PHOSphorylation enhances paclitaxel-mediated cytotoxicity .
Abstract	2	Caveolin-1 ( CAV1 ) , a highly conserved membrane-associated protein , is a putative regulator of cellular transformation .
	3	CAV1 is localized in the plasmalemma , secretory vesicles , Golgi , mitochondria , and endoplasmic reticulum membrane and associates with the microtubule cytoskeleton .
	4	Taxanes such as paclitaxel ( Taxol ) are potent anti-tumor agents that repress the dynamic instability of microtubules and arrest cells in the G(2)/M phase .
	5	Src PHOSphorylation of Tyr-14 on CAV1 regulates its cellular localization and function .
	6	We report that PHOSphorylation of CAV1 on Tyr-14 regulates paclitaxel-mediated apoptosis in MCF-7 breast cancer cells .
	7	Befitting its role as a multitasking molecule , we show that CAV1 sensitizes cells to apoptosis by regulating cell cycle progression and activation of the apoptotic signaling molecules BCL2 , p53 and p21 .
	8	We demonstrate that phosphorylated CAV1 triggers apoptosis by inactivating BCL2 and increasing mitochondrial permeability more efficiently than non-PHOSphorylated CAV1 .
	9	Furthermore , expression of p21 , which correlates with taxane sensitivity , is regulated by CAV1 PHOSphorylation in a p53 -dependent manner .
	10	Collectively , our findings underscore the importance of CAV1 phosphorylation in apoptosis and suggest that events that negate CAV1 tyrosine PHOSphorylation may contribute to anti-microtubule drug resistance .

### System Adaptability and Interactivity:

As previously described the system is web-based so it is easily accessible to any user. The system provides links to the list of PMIDs retrieved, the protein synonym use for the query, PubMed for abstracts. In addition it displays the species name if organism is mention in abstract or a MESH term, highlighted terms can be selected/deselected, feedback can be sent to correct annotation output. Currently, the PRO curators use an internal annotation system for eFIP to manually assert the results of the tool. But in the new version of eFIP (under development), any user will be able to assert the results in situ, and export the information in tab delimited format. In addition, whenever possible, protein names will be linked to UniProtKB identifiers (or possible ones).

Similarly, we will add the possibility to enter a list of PMIDs instead of being only gene based. This will allow a broader adoption by communities that are interested in the annotation of phosphorylation and/or PPI.

The tool currently works with abstracts but is also being tested for full-length articles (but only including abstract+result section to capture information that is more likely to be shown in an experiment).

### Performance:

Although some of the modules of eFIP have been previously evaluated (such as eGIFT and RLIMSP), the evaluation of the complete system is under way. We have created a first training corpus (currently approximately 450 abstracts including the annotations are for verbs for interaction such as bind, interact, associate, dissociate, complex, and dimerize). We will benchmarked the system and provide precision and recall as requested (by May 1, 2012).

### Proposed task for TRACKIII for eFIP:

1-Given a set of abstracts about a given protein (provided by external PRO curator and not yet curated using the system) (i) identify those that contain information about its phosphorylation and binding partner (PPI for that phosphorylated protein). These will be called curatable or positive set; and (ii) for curatable abstracts, extract information for phosphorylated protein and binding partner.

The task will be run manually and using the eFIP system (but not by the same curator)

Manual task: the user will be given the list of abstracts in Pubmed environment for further processing and a spreadsheet to complete the information needed as output

Using eFIP: curator would assert the curatable set of abstracts, and validate the extracted information and save the output as tab delimited text.

Input: gene name, gene ID or, for this activity, a list of PMIDs related to a given gene

Sample of PMID list for CAV1 (Caveolin 1) including both curatable and non curatable articles

11075810  
11339833  
11451957  
12036959  
12743374  
12921535  
14980511  
15466865  
16388599  
17190831  
18081315  
18789131

Output:

1-Provide a tab delimited file along with the following information sorted by curatable first:

PMIDs curatable (contain phosphorylation of the given protein and a protein binding partner) along with the following information:

PMID|curatable| phosphoprotein| site| binding partner (s)|Evidence

if the phosphorylation site is unknown a dash should be used for that field.

An example of this file based on set of curatable articles from the list above is shown here

EMID	Curatable	Phosphoprotein	Site	Binding partner	Evidence
11075810	Yes	caveolin-1	Tyr-14	Grb7	Sentence 8, 9. In support of this hypothesis , we show that PHOSphorylati Furthermore , we demonstrate that binding of Grb7 to tyrosine 14-PHOSphor
11451957	Yes	caveolin-1	Tyr-14	Grb7	Sentence 4, 13. Phosphocaveolin-1 (Tyr(P) -14) localizes within caveolae Finally , we investigated whether phosphocaveolin-1 (Tyr(P) -14) interact
12921535	Yes	caveolin-1	Tyr-14	Csk	Sentence 9. Csk binds to phosphocaveolin and should PHOSphorylate any co-
15466865	Yes	caveolin-1	Tyr-14	membrane type 1 matrix metalloproteinase (MT1-MMP)	Sentence 3. In this study This interaction requires the PHOSphorylation of caveolin-1 on tyrosine 1
16388599	Yes	caveolin-1	Tyr-14	PTP1B	Sentence 5,6. Overexpression of PTP1B decreases tyrosine 14 phosphorylat We further demonstrate that PTP1B physically associates with caveolin-1.
18789131	Yes	caveolin-1	Tyr-14	EGFR	Sentence 3, 5. Ionizing radiation resulted in src Kinase stabilization , Inhibition of EGFR by the antibody Erbitux resulted in a strong accumulati

## References

1. Arighi C, Siu A, Tudor C, Nchoutmboube J, Wu C, Shanker V. eFIP: a tool for mining functional impact of phosphorylation from literature. *Methods Molecular Biology* 2011;694:63-75.
2. Natale DA, Arighi CN, Barker WC, Blake JA, Bult CJ, Caudy M, Drabkin HJ, D'Eustachio P, Evsikov AV, Huang H, Nchoutmboube J, Roberts NV, Smith B, Zhang J, Wu CH. The Protein Ontology: a structured representation of protein forms and complexes. *Nucleic Acids Research* 2011(39(Database issue)):D539-45.