Euro BioImaging
Preparatory Phase II Project

D6.3 Report describing the utility and required updates of existing ontologies for the annotation of experimental manipulations (e.g., EFO) and cell morphologies and phenotypes (e.g., CMPO)

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Abstract

Ontologies are controlled vocabularies that can be used for annotation of defined data or scientific results. WP6 has tested the use of several ontologies that cover imaging modalities, cell and tissue constitution and phenotypes and experimental protocols. Several existing ontologies have proven quite effective for annotating data stored in the Euro-BioImaging IDR. Some datasets required the addition of new terms to existing ontologies. We report on the utility of our survey of existing resources and define where gaps must be filled in the future to ensure comprehensive annotation of experiments, imaging modalities and cell and tissue phenotypes.

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1. Introduction

In the last few years, repositories for imaging data hosted by laboratories, consortia, and even journals have emerged. Image data stored in these repositories include spatial and temporal measurements of gene expression, macromolecule localization, or phenotypes of cells, tissues, or animals and provide actual measurements of the distributions, dynamics, and changes in biological systems, as recorded from digital imaging systems. Their availability on-line helps ensure integrity and enables measurement, comparison, and interrogation ensuring that data are re-used and shared with the whole scientific community. In addition, data availability drives the development of new analysis and mining applications, improving the utility of the repositories themselves but also providing benefit to all scientists who use imaging.

A major goal of WP6 is the development and deployment of image data resources that provide public access to reference images recorded by users and Nodes of the Euro-BioImaging infrastructure. Integrating disparate, distinct datasets requires common vocabularies for annotating experimental, imaging and phenotypic metadata. If used comprehensively and correctly, common vocabularies for gene names, reagents (e.g., small molecule drugs), phenotypes and measurements can provide the basis for querying across datasets collected in different experiments, using different imaging modalities, at different imaging facilities and Nodes. Several well-developed ontologies cover at least part of these concepts and the Ontology Lookup Service (OLS; http://www.ebi.ac.uk/ols) provides an on-line resource for querying terms in a wide variety of ontologies. In this deliverable, we review this work and report on several ontologies that are candidates for use in Euro-BioImaging's data resources.

2. Ontologies for Experimental and Phenotypic Annotations

In WP6, during the construction of the Image Data Resource (IDR; http://idr-demo.openmicroscopy.org)[1] we have surveyed and tested several available ontologies for their utility in annotating reference image datasets. Most importantly, WP6 has used several existing ontologies and the resources that publish, document and support them for annotating data in the IDR. WP6 has also worked extensively with the maintainers of two major ontologies to substantially extend their coverage and range.

Reviews performed in the BioMedBridges project (http://www.biomedbridges.eu/) demonstrated that consistent annotation of cellular image data sets is required for their interoperability but that no existing ontology comprehensively covered the phenotypes observed in cellular microscopy images. A major output of BioMedBridges was the Cellular Microscopy Phenotype Ontology (CMPO, http://www.ebi.ac.uk/ols/ontologies/cmpo) to fill this gap. This species neutral ontology was built around phenotypes observed in an initial

[1] IDR originally was an abbreviation for "Image Data Repository", but the name was changed to "Image Data Resource" to reflect the accessibility of the image data, metadata and software stack.

set of high content screens and histopathology datasets[2] and is still being actively developed at the European Bioinformatics Institute. As a demonstration of CMPO's utility it was successfully used to annotate and connect high content studies collected in the Cellular Phenotype Database (http://www.ebi.ac.uk/fg/sym). Based on this utility, EuBI WP6 has used CMPO as the source of its phenotypic annotations in the IDR.

Another example of reuse involves the annotations of sample attributes, experimental methods, variables and protocols using the Experimental Factor Ontology (EFO; http://www.ebi.ac.uk/ols/ontologies/efo). EFO is a well-established, actively supported ontology designed to annotate studies in repositories at the European Bioinformatics Institute (EBI). EFO already contained the term "high content analysis of cells" but we extended this to specify "high content screen" (http://www.ebi.ac.uk/efo/EFO_0007550) and then to describe types of screen e.g. "high content screen of cells treated with a library of siRNAs", (synonym "RNAi screen", http://www.ebi.ac.uk/efo/EFO_0007551) to accurately describe studies in IDR.

In some IDR studies there are additional experimental variables and these have also been described by existing EFO terms. For example, in idr0003-breker-plasticity (http://idr-demo.openmicroscopy.org/webclient/?show=screen-51), protein localization was measured after the cells were grown under different stress conditions and the EFO term "environmental stress" was used to describe the type of experimental condition. Sample attributes such as cell lines and ecotypes/cultivars for plants can also be tagged with EFO terms. Growth, treatment, data acquisition and data processing protocols are recorded for each study and ontology terms have been used to describe the type of protocol. Some, such as growth and treatment protocol terms already existed in EFO while others such as "HCS image acquisition and feature extraction protocol" (http://www.ebi.ac.uk/efo/EFO_0007572) have been added. We were able to successfully propose additional terms through the EBI's JIRA ticketing system, as for EFO. Terms such as protein localization phenotypes, which follow a standard ontology pattern, can also be quickly added to the ontology using the Webulous (https://www.ebi.ac.uk/efo/webulous/) term submission system. Further study and protocol types for non-high content screen studies will need to be added in the future, e.g. protein localization using 3D-SIM (http://idr-demo.openmicroscopy.org/webclient/?show=image-1884820). Overall, while EFO was not explicitly designed to support cell and tissue phenotyping studies, it has proven quite useful for describing several aspects of the experimental designs and protocols of studies included in the IDR.

To annotate organismal and imaging metadata, we have used the NCBI Taxonomy, the comprehensive species resource, (http://www.ebi.ac.uk/ols/ontologies/ncbitaxon) and the Biological Imaging Methods ontology (Fbbi, http://www.ebi.ac.uk/ols/ontologies/fbbi) respectively. Fbbi was chosen because it gives good coverage of imaging methods, is used by other resources such as the CELL Image Library, PhenoImageShare, and Virtual Fly Brain

[2] Jupp et al, (2016) J Biomed Semantics, 7:28; 10.1186/s13326-016-0074-0

and also covers sample preparation and visualization methods which may be added to study annotations in future. However, our evaluation of Fbbi revealed that it does not yet cover concepts that are crucial for Euro-BioImaging, e.g., super-resolution microscopy. This ontology is not actively maintained so adding new terms is not straightforward and alternatives should be investigated e.g. the Chemical Methods Ontology (http://www.ebi.ac.uk/ols/ontologies/chmo) or the eagle-I resource ontology (http://www.ebi.ac.uk/ols/ontologies/ero) both of which include some imaging methods. The Ontology for BioMedical Investigations may also be expanded to include more imaging related terms. Other initiatives such as the Quantitative Histopathology Imaging Ontology (http://dx.doi.org/10.1016/j.jbi.2016.12.006) may provide good descriptive terms for specific types of studies.

3. Complex Phenotype Annotation

In our survey of studies submitted to the IDR, we found several examples of authors using complex statements to report their results. Examples are 'viable spheroid vegetative cell', 'cell shape round or non-adherent'. The terms used by different authors can be normalized by linking to ontology terms. For example 'viable spheroid vegetative cell', 'cell shape round or non-adherent' and 'low eccentricity cells' can all be tagged with the ontology term of 'round cell phenotype' (CMPO_0000118). This enables links to be made between datasets in which different terminology is used to describe essentially the same phenotype (see http://idr-demo.openmicroscopy.org/mapr/phenotype/?value=CMPO_0000118) and from this genes associated with these phenotypes in the different studies can be identified and studied in more detail. As noted above, WP6's work on the IDR makes heavy use of CMPO and EFO, largely because they were established, in use and supported. However, some phenotypes observed, such as gene expression patterns in plant tissues, are beyond the scope of CMPO and no suitable ontology has yet been identified to describe this data.

Appendix 1 summarises WP6's experience with existing annotation resources and lists the terms it has added to EFO and CMPO. Overall, WP6 has had good success reusing and extending the work performed in BioMedBridges and other predecessor projects. However, there are several types of imaging and phenotypic studies that are not yet covered by defined terms, which highlights the requirement for new efforts to expand and improve these critical resources.

4. Using Ontology Annotations in IDR

Once appropriate annotations for the various components of phenotypic data have been defined, the image data have to be annotated and applications that store the annotations and provide useful querying tools and interfaces have to be built. These have been built into IDR and are now publically available. For example author submitted phenotypes can be queried by keyword (http://idr-demo.openmicroscopy.org/mapr/phenotype/?value=elongated&query=true). There is also

support for querying individual CMPO annotations (http://idr-demo.openmicroscopy.org/mapr/phenotype/?value=CMPO_0000077). This facility combines metadata storage in OMERO with query and metadata mapping enabled by an OMERO plug-in called MAPR. These technologies will be described in detail in a future deliverable reporting on the architecture and deployment of the IDR.

5. Using Ontology Annotations in Medical Imaging

In the field of Medical Imaging, the benefits of ontologies to scientific discovery become more evident when applied at large scale. Therefore, a critical component of current and future efforts will be the aggregation and organization of the Medical Image data in the scientific field. Currently, the main efforts are directed to the development of machine-readable standards to represent neuroimaging data which is where further advances are being made in this field (e.g., the Neuroimaging Data Model, http://www.nidm.nidash.org); creating reproducible, shareable open-source analysis pipelines Data Model (eg, the Nipype framework[3]); the establishment of open resources to share both raw fMRI datasets (eg OpenfMRI[4]) and statistical images (e.g., NeuroVault; http://www.neurovault.org). Another important effort in this field is the Brain Imaging Data Structure (BIDS). BIDS (http://bids.neuroimaging.io) is a simple and intuitive way to organize and describe the neuroimaging and behavioral data. A good introduction to the BIDS standard can be found in http://www.nature.com/articles/sdata201644. To conclude, integrated data repositories are becoming an essential resource that allow, among other things, rational management of biomedical and health data collected from the multiple sources of the Electronic Clinical Record (EHR)[5] for reuse in clinical management and improvement of quality of care and research[6,7,8].

6. Conclusion

WP6 has identified several existing ontologies that are appropriate for authoritatively annotating image data submitted to Euro-BioImaging IDR. The CMPO and EFO resources are particularly useful as they provide many appropriate ontology terms and are well supported allowing for the addition of new terms. Several medically-related ontologies have similar characteristics.

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[3] Gorgolewski K, Burns CD, Madison C, Clark D, Halchenko YO, et al. 2011. Nipype: a flexible, lightweightand extensible neuroimaging data processing framework in Python. Front. Neuroinform. 5:13

[4] Poldrack RA, Barch DM, Mitchell JP, Wager TD, Wagner AD, et al. 2013. Toward open sharing of task-based fMRI data: the OpenfMRI project. Front. Neuroinform. 7:12

[5] L. Toubiana and M. Cuggia, Big Data and Smart Health Strategies: Findings from the Health Information Systems Perspective. IMIA Yearbook. 2014;9(1):125–7.

[6] Dixon BE, Rosenman M, Xia Y, Grannis SJ. A vision for the systematic monitoring and improvement of the quality of electronic health data. Stud Health Technol Inform. 2013;192:884-8.

[7] Satagopam, Venkata et al. “Integration and Visualization of Translational Medicine Data for Better Understanding of Human Diseases.” Big Data 4.2 (2016): 97–108. PMC. Web. 29 Dec. 2016.

[8] Martin-Sanchez, F., and K. Verspoor. “Big Data in Medicine Is Driving Big Changes.” Yearbook of Medical Informatics 9.1 (2014): 14–20. PMC. Web. 29 Dec. 2016.

There does not yet exist a single available ontology that captures all of the information that Euro-BioImaging requires for annotating the data it stores and publishes for the scientific community. In particular there are not yet good definitions of the wide range of imaging modalities that Euro-BioImaging Nodes support now, will build and deliver in the future and will make available through the Euro-BioImaging Web Access Portal. A major priority for future development should be either the establishment of resources for development and adoption of existing resources like Fbbi, or for development of a new ontology that properly describes the wide range of modalities and methods covered by biological and biomedical imaging. Nonetheless, it is encouraging that the outputs of several previous projects have been tested and proven useful for annotating and querying Euro-BioImaging data. WP6 recommends that as Euro-BioImaging moves towards construction, it devote resources for the establishment and maintenance of annotation tools required to properly define and annotate Euro-BioImaging technology and data. This is essential for Euro-BioImaging's resources to become globally used scientific references.

Appendix 1 - Ontology terms used in IDR annotation

Ontology terms used in IDR annotation, including their source and whether the term existed already or was added as part of the annotation of data in IDR.

Ontology	Term used in IDR	Existing term or added to ontology as part of IDR project
NCBITaxon	Homo sapiens (NCBITaxon_9606)	existing
NCBITaxon	Arabidopsis thaliana (NCBITaxon_3702)	existing
NCBITaxon	Drosophila melanogaster (NCBITaxon_7227)	existing
NCBITaxon	Schizosaccharomyces pombe (NCBITaxon_4896)	existing
NCBITaxon	Saccharomyces cerevisiae (NCBITaxon_4932)	existing
NCBITaxon	Mus musculus (NCBITaxon_10090)	existing
EFO	high content analysis of cells (EFO_0005397)	existing
EFO	growth protocol (EFO_0003789)	existing
EFO	treatment protocol (EFO_0003969)	existing
EFO	Environmental Stress (EFO_0000470)	existing
EFO	genotype (EFO_0000513)	existing
EFO	Cell Line (EFO_0000322)	existing
EFO	organism part (EFO_0000635)	existing
EFO	Antibody (EFO_0000264)	existing
EFO	sex (PATO_0000047)	existing
EFO	individual (EFO_0000542)	existing
EFO	media (EFO_0000579)	existing
EFO	compound (CHEBI_37577)	existing
EFO	dose (EFO_0000428)	existing
EFO	time (EFO_0000721)	existing
EFO	RNA interference (GO_0016246)	existing
EFO	HeLa (EFO_0001185)	existing
EFO	S2R+ (EFO_0005837)	existing
EFO	U2OS (EFO_0002869)	existing
EFO	MDA-MB-231 (EFO_0001209)	existing
EFO	Hep3B (EFO_0002205)	existing
EFO	HS578T (EFO_0001192)	existing
EFO	T47D (EFO_0001247)	existing
EFO	MDA-MB-157 (EFO_0001206)	existing
EFO	HCC1143 (EFO_0001169)	existing
EFO	AU565 (EFO_0001087)	existing
EFO	ZR75.1 (EFO_0001262)	existing
EFO	CAMA1 (EFO_0001100)	existing

EFO	BT474 (EFO_0001093)	existing
EFO	MDA-MB-231 (EFO_0001209)	existing
EFO	SKBR3 (EFO_0001236)	existing
EFO	JIMT1 (EFO_0005388)	existing
EFO	MCF7 (EFO_0001203)	existing
EFO	MDA-MB-453 (EFO_0001215)	existing
EFO	HCC1954 (EFO_0001175)	existing
EFO	HCC70 (EFO_0001181)	existing
EFO	SUM149 (EFO_0001240)	existing
EFO	SUM159 (EFO_0001241)	existing
EFO	MCF10A (EFO_0001200)	existing
EFO	MCF12A (EFO_0001202)	existing
EFO	high content screen (EFO_0007550)	added
EFO	primary high content screen (synonym: primary screen) (EFO_0007556)	added
EFO	secondary high content screen (synonym: secondary screen) (EFO_0007557)	added
EFO	validation high content screen (synonym: validation screen)(EFO_0007558)	added
EFO	high content screen of cells in a gene deletion library (synonym:gene deletion screen) (EFO_0007552)	added
EFO	high content screen of cells in treated with a compound library (synonym: compound screen) (EFO_0007553)	added
EFO	high content screen of cells treated with library of siRNAs (synonym: RNAi screen) (EFO_0007551)	added
EFO	high content analysis of cells by molecular content (synonym: protein screen) (EFO_0005398)	added
EFO	haploid deletion library (EFO_0007561)	added
EFO	diploid homozygous deletion library (EFO_0007562)	added
EFO	GFP protein fusion library (EFO_0007566)	added
EFO	HA-Flag protein fusion library (EFO_0007568)	added
EFO	siRNA library (EFO_0007564)	added
EFO	compound library (EFO_0007569)	added
EFO	HCS library protocol (EFO_0007571)	added
EFO	HCS image acquistion and feature extraction protocol ((EFO_0007572)	added
EFO	HCS data analysis protocol (EFO_0007573)	added
FBbi	bright-field microscopy (FBbi_00000243)	existing

FBbi	fluorescence microscopy (FBbi_00000246)	existing
FBbi	confocal microscopy (FBbi_00000251)	existing
FBbi	spinning disk confocal microscopy (FBbi_00000253)	existing
FBbi	structured illumination microscopy (SIM) (FBbi_00000332)	existing
CMPO	abnormal cell cycle phenotype (CMPO_0000212)	existing
CMPO	abnormal cell growth phenotype (CMPO_0000316)	existing
CMPO	abnormal cell shape phenotype (CMPO_0000116)	existing
CMPO	abnormal chromosome segregation phenotype (CMPO_0000326)	existing
CMPO	abnormal nucleus shape phenotype (CMPO_0000157)	existing
CMPO	absence of cell spreading phenotype (CMPO_0000324)	existing
CMPO	absence of mitotic chromosome decondensation phenotype (CMPO_0000216)	existing
CMPO	absence of mitotic process phenotype (CMPO_0000217)	existing
CMPO	actin cytoskeleton phenotype (CMPO_0000283)	existing
CMPO	actin filament phenotype (CMPO_0000104)	existing
CMPO	actin nuclear ring phenotype (CMPO_0000302)	existing
CMPO	aggregated cells in population (CMPO_0000049)	existing
CMPO	aggregated microtubules phenotype (CMPO_0000286)	existing
CMPO	apoptopic nucleus phenotype (CMPO_0000112)	existing
CMPO	apoptotic cell shape phenotype (CMPO_0000048)	existing
CMPO	apoptotic DNA (CMPO_0000262)	existing
CMPO	asymmetric lamellipodia phenotype (CMPO_0000266)	existing
CMPO	bilobed nucleus phenotype (CMPO_0000117)	existing
CMPO	binuclear cell phenotype (CMPO_0000213)	existing
CMPO	bright nuclear body phenotype (CMPO_0000335)	existing
CMPO	bright nuclei phenotype (CMPO_0000154)	existing
CMPO	cell adhesion phenotype (CMPO_0000028)	existing
CMPO	cell apoptosis phenotype (CMPO_0000220)	existing
CMPO	cell component morphology phenotype (CMPO_0000303)	existing
CMPO	cell component size phenotype (CMPO_0000010)	existing
CMPO	cell component structure phenotype (CMPO_0000012)	existing

CMPO	cell death phenotype (CMPO_0000030)	existing
CMPO	cell DNA phenotype (CMPO_0000176)	existing
CMPO	cell morphology phenotype (CMPO_0000005)	existing
CMPO	cell projection phenotype (CMPO_0000280)	existing
CMPO	cell spreading phenotype (CMPO_0000188)	existing
CMPO	cell with projections (CMPO_0000071)	existing
CMPO	cell-matrix adhesion phenotype (CMPO_0000185)	existing
CMPO	cellular component phenotype (CMPO_0000259)	existing
CMPO	cilium morphology phenotype (CMPO_0000252)	existing
CMPO	decreased axon thickness phenotype (CMPO_0000224)	existing
CMPO	decreased cell numbers (CMPO_0000052)	existing
CMPO	decreased cell size phenoptype (CMPO_0000129)	existing
CMPO	decreased cortical actin cytoskeleton mass phenotype (CMPO_0000273)	existing
CMPO	decreased duration of mitotic prophase phenotype (CMPO_0000329)	existing
CMPO	decreased lamellipodia width phenotype (CMPO_0000277)	existing
CMPO	decreased nucleus size phenotype (CMPO_0000141)	existing
CMPO	decreased number of actin filament phenotype (CMPO_0000106)	existing
CMPO	decreased number of filopodia phenotype (CMPO_0000067)	existing
CMPO	decreased number of microtubules phenotype (CMPO_0000068)	existing
CMPO	disorganised cortical actin cytoskeleton phenotype (CMPO_0000274)	existing
CMPO	disorganized microtubules phenotype (CMPO_0000147)	existing
CMPO	elongated cell phenotype (CMPO_0000077)	existing
CMPO	fan-shaped lamellipodia phenotype (CMPO_0000278)	existing
CMPO	fewer aggregated cells in population phenotype (CMPO_0000416)	existing
CMPO	fewer cells with projections (CMPO_0000075)	existing
CMPO	geometric cell phenotype (CMPO_0000261)	existing
CMPO	graped micronucleus phenotype (CMPO_0000156)	existing
CMPO	increased actin localised to the cytoplasm (CMPO_0000296)	existing
CMPO	increased actin localised to the nucleus	existing

	(CMPO_0000294)	
CMPO	increased amount of punctate actin foci phenotype (CMPO_0000291)	existing
CMPO	increased amount of stress fibers located in the cell cortex phenotype (CMPO_0000297)	existing
CMPO	increased amount of stress fibers phenotype (CMPO_0000289)	existing
CMPO	increased amount of transverse stress fibers (CMPO_0000298)	existing
CMPO	increased amount of zig-zag stress fibers (CMPO_0000299)	existing
CMPO	increased cell component number phenotype (CMPO_0000042)	existing
CMPO	increased cell movement distance (CMPO_0000237)	existing
CMPO	increased cell movement speed (CMPO_0000236)	existing
CMPO	increased cell numbers (CMPO_0000051)	existing
CMPO	increased cell size in population (CMPO_0000340)	existing
CMPO	increased cell size phenotype (CMPO_0000128)	existing
CMPO	increased cilium length phenotype (CMPO_0000133)	existing
CMPO	increased cortical actin cytoskeleton mass phenotype (CMPO_0000272)	existing
CMPO	increased duration of mitotic prophase phenotype (CMPO_0000328)	existing
CMPO	increased lamellipodia width phenotype (CMPO_0000276)	existing
CMPO	increased microtubule-based processes phenotype (CMPO_0000351)	existing
CMPO	increased nucleus size phenotype (CMPO_0000140)	existing
CMPO	increased number of actin filament phenotype (CMPO_0000105)	existing
CMPO	increased number of filopodia (CMPO_0000076)	existing
CMPO	increased number of microtubules phenotype (CMPO_0000097)	existing
CMPO	increased rate of protein secretion (CMPO_0000246)	existing
CMPO	increased thickness of dendritic branches phenotype (CMPO_0000145)	existing
CMPO	increased variability of cell shape in population (CMPO_0000270)	existing

CMPO	increased variability of cell size in population (CMPO_0000269)	existing
CMPO	increased variability of nuclear shape in population (CMPO_0000345)	existing
CMPO	lamellipodium phenotype (CMPO_0000279)	existing
CMPO	layered cells in population (CMPO_0000282)	existing
CMPO	loss of cell monolayer (CMPO_0000293)	existing
CMPO	M phase arrested phenotype (CMPO_0000196)	existing
CMPO	M phase mitotic phenotype (CMPO_0000265)	existing
CMPO	metabolic process phenotype (CMPO_0000037)	existing
CMPO	metaphase arrested phenotype (CMPO_0000305)	existing
CMPO	metaphase delayed phenotype (CMPO_0000307)	existing
CMPO	microtubule spindle morphology phenotype (CMPO_0000376)	existing
CMPO	microtubules nuclear bracket phenotype (CMPO_0000287)	existing
CMPO	microtubules nuclear ring phenotype (CMPO_0000288)	existing
CMPO	mild decrease in rate of protein secretion (CMPO_0000318)	existing
CMPO	misshapen DNA (CMPO_0000177)	existing
CMPO	mitosis arrested (CMPO_0000338)	existing
CMPO	mitosis delayed phenotype (CMPO_0000202)	existing
CMPO	mitotic chromosome condensation phenotype (CMPO_0000218)	existing
CMPO	mitotic metaphase plate congression phenotype (CMPO_0000348)	existing
CMPO	more cells in M phase (CMPO_0000263)	existing
CMPO	more lamellipodia cells (CMPO_0000083)	existing
CMPO	more multinucleate cells (CMPO_0000300)	existing
CMPO	no cells phenotype (CMPO_0000301)	existing
CMPO	nuclear morphology phenotype (CMPO_0000249)	existing
CMPO	polylobed nuclear phenotype (CMPO_0000357)	existing
CMPO	polyploid cell phenotype (CMPO_0000086)	existing
CMPO	proliferating cells (CMPO_0000241)	existing
CMPO	prometaphase arrested phenotype (CMPO_0000343)	existing
CMPO	prometaphase delayed phenotype (CMPO_0000344)	existing
CMPO	pyknotic nuclear phenotype (CMPO_0000341)	existing
CMPO	regulation of metabolic process phenotype (CMPO_0000039)	existing

CMPO	round cell phenotype (CMPO_0000118)	existing
CMPO	round nucleus phenotype (CMPO_0000123)	existing
CMPO	S phase mitotic phenotype (CMPO_0000087)	existing
CMPO	star shaped cell phenotype (CMPO_0000267)	existing
CMPO	strong decrease in rate of protein secretion (CMPO_0000319)	existing
CMPO	triangular shaped cell phenotype (CMPO_0000122)	existing
CMPO	abnormal microtubule cytoskeleton morphology during mitotic interphase (CMPO_0000438)	added
CMPO	abnormal mitotic cell cycle phase phenotype (CMPO_0000437)	added
CMPO	absence of protein localized in bud neck phenotype (CMPO_0000439)	added
CMPO	cell response to DNA damage phenotype (CMPO_0000415)	added
CMPO	cellular response to chemical stimulus phenotype (CMPO_0000421)	added
CMPO	curved cell phenotype (CMPO_0000365)	added
CMPO	decreased level of polypetide in cell nucleus (CMPO_0000434)	added
CMPO	elongated cytoplasmic microtubules phenotype (CMPO_0000370)	added
CMPO	fan-shaped cell phenotype (CMPO_0000428)	added
CMPO	fewer cells with G1 phase microtubule arrays phenotype (CMPO_0000410)	added
CMPO	fewer cells with interphase microtubule arrays phenotype (CMPO_0000388)	added
CMPO	fewer cells with metaphase microtubule spindles phenotype (CMPO_0000387)	added
CMPO	increased level of polypetide in cell nucleus (CMPO_0000433)	added
CMPO	increased number of microtubule bundle phenotype (CMPO_0000372)	added
CMPO	kinetochore phenotype (CMPO_0000427)	added
CMPO	more cells with G1 phase microtubule arrays phenotype (CMPO_0000412)	added
CMPO	more cells with interphase microtubule arrays phenotype (CMPO_0000383)	added
CMPO	more cells with metaphase microtubule spindles phenotype (CMPO_0000378)	added
CMPO	more cells with S phase microtubule arrays phenotype (CMPO_0000413)	added
CMPO	negative regulation of protein import into	added

	nucleus phenotype (CMPO_0000435)	
CMPO	pear-shaped cell phenotype (CMPO_0000366)	added
CMPO	positive regulation of protein import into nucleus phenotype (CMPO_0000436)	added
CMPO	protein localized in bud neck phenotype (CMPO_0000391)	added
CMPO	protein localized in Cajal body phenotype (CMPO_0000404)	added
CMPO	protein localized in cell periphery phenotype (CMPO_0000392)	added
CMPO	protein localized in centrosome phenotype (CMPO_0000425)	added
CMPO	protein localized in cytosol phenotype (CMPO_0000393)	added
CMPO	protein localized in endoplasmic reticulum phenotype (CMPO_0000394)	added
CMPO	protein localized in mitochondrion phenotype (CMPO_0000395)	added
CMPO	protein localized in nuclear periphery phenotype (CMPO_0000396)	added
CMPO	protein localized in nuclear pore phenotype (CMPO_0000426)	added
CMPO	protein localized in nuclear speckle phenotype (CMPO_0000405)	added
CMPO	protein localized in nucleolus phenotype (CMPO_0000397)	added
CMPO	protein localized in nucleus phenotype (CMPO_0000398)	added
CMPO	protein localized in paraspeckle phenotype (CMPO_0000406)	added
CMPO	protein localized in PML body phenotype (CMPO_0000407)	added
CMPO	protein localized in polycomb body phenotype (CMPO_0000408)	added
CMPO	protein localized in punctate foci phenotype (CMPO_0000400)	added
CMPO	protein localized in Sam68 nuclear body phenotype (CMPO_0000409)	added
CMPO	protein localized in vacuolar membrane phenotype (CMPO_0000402)	added
CMPO	protein localized in vacuole phenotype (CMPO_0000401)	added
CMPO	S-shaped cell phenotype (CMPO_0000364)	added
CMPO	shortened cytoplasmic microtubules phenotype	added

	(CMPO_0000371)	
CMPO	stubby cell phenotype (CMPO_0000367)	added
CMPO	telophase arrested phenotype (CMPO_0000424)	added