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Overview of nuclear bodies and their classification in the *Terminologia Histologica*

Running title*: **Nuclear bodies-Terminologia Histologica***

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The work was conducted in Center of Excellence in Morphological and Surgical Studies, Universidad de La Frontera, Temuco, Chile.

Abstract

Background: Nuclear bodies are membrane-less subnuclear organelles that perform important functions in the cell, such as transcription, RNA splicing, processing and transport of ribosomal pre-RNA, epigenetic regulation, and others. The aim of the work was to analyze the classification of nuclear bodies in the *Terminologia Histologica* and biological and bibliographical databases.

Materials and methods: The semantic structure of the *Nucleoplasm* section in the *Terminologia Histologica* was analyzed and unsystematic bibliographical search was made in the *Pubmed*, *Scielo,*

EMBASE databases and *European Bioinformatics Institute* (EMBL-EBI) biology database to identify which structures are classified as NB.

Results: It was found that the terms *Corpusculum convolutum*, *Macula interchromatinea* and *Corpusculum PML* are not correctly classified in the *Terminologia Histologica*, since they are subordinated under the term *Chromatinum* and not under *Corpusculum nucleare*. The bibliography consulted showed that 100%, 92.6% and 81.5% of articles mentioned *Corpusculum convolutum*, *Macula interchromatinea* and *Corpusculum PML* respectively as nuclear bodies.

Conclusions: It is suggested to relocate the terms Corpusculum convolutum, Macula interchromatinea and Corpusculum PML with the name of Corpusculum nucleare and the incorporation of two new entities to the Histological Terminology according to the information collected: *paraspeckles* and *histone locus body.*

Key words: nuclear bodies, *Terminologia Histologica*, coiled bodies, PML nuclear bodies, nuclear speckles

Introduction

The different morphology terminologies (*Anatomica*, *Histologica* and *Embryologica*) seek uniformity of terms to transmit the new knowledge clearly in each area. In addition to this aim, their semantic structure categorizes and increases the intrinsic meaning of each term, since they contribute information about the relations that exist among them, allowing the reader to infer knowledge [38].

One of the most complex organelles within the cell structure is the nucleus, which is highly organized and contains several subnuclear compartments, including nuclear bodies (NB). NB were first described by Thé in 1960 and designated as such by Weber & Frommes in 1963. The first descriptions categorized them based on their size and ultrastructural characteristics into Types I, II, III, IV and V without a defined name [2, 10]. Other authors added to the classification of Bouteille *et al.* with simple and complex categories, adding a greater degree of classification [2]. NB are defined as intranuclear

domains of differing sizes, in dynamic constant, that are found in the cell in both normal and pathological conditions [2, 4, 29, 52]. Located in the nucleoplasm, they compartmentalize the interchromatin region, concentrating reactants and substrates, creating microenvironments to carry out specialized functions like transcription, RNA splicing, processing and transport of ribosomal pre-RNA, gene silencing and others. Unlike cytoplasmic organelles, NB are not confined by a membranous structure, which made its definition even more complicated. They can be visualized by confocal and fluorescence microscopy or by electronic microscopy. NB are made up of RNA and proteins, and hold their structure by the interactions existing between them: RNA-protein or protein-protein. These proteins are constantly exchanged with the nucleoplasm regulated by post-translational modifications like phosphorylation and SUMOylation [38], there being proteins common to different NB and others specific of a certain type of NB [3, 29, 39, 47, 55]. With respect to the formation of NB, three models are considered: The first is the model of stochastic assembly where the components of the NB are grouped without a defined order; the assembly is random. The second model is an ordered assembly, where the components are assembled sequentially and dependent on interaction between the components, with a hierarchical order. The third model is the seeding assembly, a mixture of the previous models, where one or a few components are assembled hierarchically and the rest stochastically [12, 29]. Another line of research studies the assembly and disassembly of NB from a physical perspective, and propose that NB are formed through a liquid-liquid transition phase [9], forming structures that pass proteins from a dispersed nucleoplasmic state to a localized state in the NB and vice versa. These interactions would be affected by the same parameters that govern the free energy of protein interactions, salt concentration, proteins concentration and temperature [50, 53], which agrees with the stochastic hypothesis of assembly that Mao *et al.* (2011) suggest. The diversity of NB has increased over the years. There is an extensive bibliography that mentions *Corpusculum convulutum (coiled body)* [21, 35, 45], *Corpusculum PML* (PML nuclear body) [25, 35, 45], *Granulum interchromatineum* (interchromatin granule) and Macula *interchromatinea* (nuclear speckle; interchromatin granule cluster) [20, 35, 45, 46] as NB currently included in the *Terminologia Histologica* (TH) [15] and other NB included in new sources of knowledge such as biological and bibliographical databases that are not included in the TH and therefore have no Latin term. These include **paraspeckles** [17, 18, 40, 45, 55], ***cleavage body*** [27, 40, 41, 45, 55], **histone locus body** [30, 40, 48, 55], **Gemini of coiled bodies or gems nuclear body** [21, 28, 35, 40, 55] and **Polycomb body**

[35, 40, 44, 45]. Other NB have been described only in certain cell types, like **nuclear dicing body or D-bodies** described in plants [14] and other NB described in particular cell states as transient organelles, like **stress nuclear body** present in cells under stress conditions [8, 35, 40, 45], the **Clastosomes** [5,45] formed in response to a sudden increase in protein levels for proteasome-dependent proteolysis in the nucleus and the **Oct1/PTF/transcription (OPT) domain**, which are large nuclear domains where transcription factors are concentrated [5, 45]. The existing bibliography to date is not uniform as to which structures are considered NB. Some authors consider NB to be those that are always present in the cell such as the nucleolus, *coiled body*, group of interchromatin granules or speckles and PML nuclear bodies, whereas others also consider those structures that comply morphological criteria but are present transiently in the cell as clastosomes. A review of the TH [15] reveals that the NB are located under the term *Chromatinum* (H1.00.01.2.02004) and not under the term *Corpusculum nucleare* (H1.00.01.2.02019). As a result, anyone accessing the terminology and not familiar with the topic could wrongly conclude that NB are part of the chromatin and not the nucleoplasm. Bearing this in mind, the aims of this study were to analyze the semantic structure of the terms in the Nucleoplasm section, Cytology chapter in the TH in order to propose changes in the order of the terms related to NB to avoid errors derived from their incorrect location, and to perform a bibliographical review to identify whether there are other NB that could be included in the TH.

Materials and methods

The semantic structure of the *Nucleoplasm* section (H1.00.01.2.02001) in the "*Terminologia Histologica*: International terms for human cytology and histology" [15] was analyzed and assessed, considering whether or not the NB are duly listed under the term *Corpusculum nucleare* (H1.00.01.2.02019) or not. Additionally, an unsystematic bibliographical search was made of scientific articles in the *Pubmed, Scielo and EMBASE* databases of last the 20 years to identify which structures are classified as NB. The key words used were "subnuclear structure" OR "nuclear subcompartment" OR "nuclear bodies". The selection included those articles that informed the classification of NB in their title and abstract. The search was also made in the *European Bioinformatics Institute* (EMBL-EBI) biology database, *QuickGO* section [54], which included those structures as belonging to the terms

"Nuclear body" and "Nuclear chromatin". The information collected was recorded in a table, considering the percentage of which NB were mentioned in the selected articles.

Results

In the TH, the term *Corpusculum nucleare* (H1.00.01.2.02019) is in the chapter *Cytologia* (Cytology), which is subdivided into *Cellula* (Cell) and *Cyclus cellularis* (Cell cycle). It is precisely in the item *Cellula*, *Nucleoplasma* section (H1.00.01.2.02001) together with the other two terms, *Lamina fibrosa nuclearis* (H1.00.01.2.02002) and *Chromatinum* (H1.00.01.2.02004). The NB *Granulum interchromatineum* (H1.00.01.2.02013), *Macula interchromatinea* (H1.00.01.2.02014), *Corpusculum convolutum* (H1.00.01.2.02015) and *Corpusculum PML* (H1.00.01.2.02011) are listed under the term *Chromatinum*. For the term *Corpusculum nucleare*, there are no subordinate structures (Table I).

Considering the terms "subnuclear structure" OR "nuclear subcompartment" OR "nuclear bodies" in the Pubmed, ScieLo and EMBASE databases, 26 articles were selected that refer specifically to the classification of NB, those articles that referred to only one NB in particular were not selected. It was found that 100% of the articles selected mentioned *Corpusculum convolutum* as a NB, 96.15% mentioned *Macula interchromatinea* and 84.61% *Corpusculum PML* (Tabla II). None of the articles mentioned *Fibrilla perichromatiean* or *Chromatinum sexuale* as a NB. The term *Granulum interchromatineum* was mentioned as part of *Macula interchromatinea* (Table II). In the articles selected other structures catalogued as NB were also described, it being found that four were mentioned 50% or more of the time (Table II). In the European Bioinformatics Institute (EMBL-EBI) database, *QuickGO* section, under the term "Nuclear body", the terms *Corpusculum convulutum* (Coiled body), *Corpusculum PML* (PML nuclear body), *Granulum interchromatineum* (Interchromatin granule) and *Macula interchromatinea* (Nuclear speckle; Interchromatin granule cluster) were found, which are currently present in the TH as part of *Nucleoplasma* (H1.00.01.2.02001) but under the term *Chromatinum* (H1.00.01.2.02004) (Fig. 1).

Discussion

In last years studies on the morphology and function of NB have advanced significantly [9, 49, 53]; however, controversy remains and it is not yet clear what functions each of them fulfills. Unfortunately, this lack of information could negatively impact on the location of NB-related terms in the TH as well as on the incorporation of new terms. As an example of the importance of this information, the TH [15] makes observations of some NB in footnotes, such as *Macula interchromatinea,* where it clarifies that "these particles are not true granules, but rather spots obtained after the immunological identification of snRNP complex proteins", *Corpusculum convolutum*, which it describes as an accessory coiled body of the nucleolus, and *Corpusculum PML*, which it describes as a promyelocytic leukemia nuclear body, calling it a nuclear body that "is generally present in all mammalian cells and are at least necessary for the normal differentiation of promyelocytes". Incredibly, despite this information given at the bottom of the page, the location of the terms related to the NB in the *Nucleoplasma* section (H1.00.01.2.02001) in the TH is incorrect, as they are placed under the term *Chromatinum* (H1.00.01.2.02004) and not under *Corpusculum nucleare* (H1.00.01.2.02019). For this reason, one of the aims of this study was to analyze the semantic structure of the terms in the *Nucleoplasma* section (H1.00.01.2.02001) in the TH in order to propose changes in the location of NB-related terms to avoid errors derived from their incorrect location. In this respect, several studies, before and after the 2008 edition of theTH, placed *Macula interchromatinea*, *Corpusculum convolutum* and *Corpusculum PML* [Strouboulis & Wolffe, 1993, 29, 31, 35, 40] under the common name of NB, which would support the proposal to place these structures under the term *Corpusculum nucleare.* On the other hand, it is proposed that the term *Granulum interchromatineum* be placed under the term *Macula interchromatinea* (Table III), since studies show that this NB is composed of interchromatin granules from 20 to 25 nm connected by a thin fibril that gives it the appearance of a pearl necklace [46].

With respect to the term *Fibrilla perichromatinea,* the literature does not clarify its classification. Considering its morphology, it is defined as a structure that forms part of the heterochromatin, located on its edge, and could possibly present continuity with the *Granulum interchromatineum* structure [37]. This agrees with the indication given by the *European Bioinformatics Institute* (EMBL-EBI), since in the *QuickGO* [55] section they describe it with code GO:0005727 as part of the nuclear chromatin. Yet from a functional point of view, *Fibrilla perichromatinea* behaves like a NB. In this regard, Puvio & Money (1981) reported that this structure has a function in the production of heterogeneous nuclear

RNA (hnRNA), which agrees with Elliott & Michael (2016), who consider *Fibrilla perichromatinea* a subnuclear site enriched in factors where the splicing of nascent messenger RNA begins, classifying it in the same category as other recognized NB like *Nucleoli* and *Cospusculum convulutum.* Based on the foregoing, one of the alternatives to follow could be that the term *Fibrilla perichromatinea* should be placed under *Heterochromatinum*, since it is part of it, and perhaps a footnote should be added indicating that functionally speaking, it fulfills a role similar to that of other recognized NB.

With respect to the identification of other NB in the selected articles and which are not included in the TH, we observed that paraspeckles were mentioned in 80.76% of the articles, the histone locus body in 57.69%, the Gems nuclear body in 53.84% and the Polycomb body in 50%. Paraspeckles were first described as an electron dense structure associated with *Macula interchromatinea* together with proteins PSPC1, NONO and SFPQ and long noncoding RNA NEAT1 as marker molecules [17, 18]. The function of paraspeckles has been studied in recent years, defining them as a subnuclear organelle for the storage and processing of RNA and the retention of hyperedited messenger RNA, relating them to the stress response, circadian rhythm and viral infection; they have even been related to cell differentiation [13, 18, 29, 49]. The histone locus body is a nuclear domain enriched in the transcription factors needed for the expression and processing of the pre-messenger RNA in replication-dependent histone genes in close proximity to *Corpusculum convolutum*. Years ago it was thought that these were the same entity; however, current molecular technology has shown that they are different nuclear domains [30, 34]. The Gems nuclear body is a nuclear structure close to or in interaction with *Corpusculum convolutum*, which has the SMN (survival of motor neurons) protein, geminin-2 and geminin-3 as marker molecules [21, 28] and, finally, the Polycomb body is a nuclear domain where the epigenetic regulatory Polycomb group (PcG) proteins are concentrated and organize, the function of which is to regulate the expression of various genes involved in controlling the cell cycle, senescence, differentiation of stem cells and others. There are two repressive complexes: Polycomb repressive complex 1 (PRC1) and Polycomb repressive complex 2 (PRC2); these work in cooperation for epigenetic regulation [29, 44].

Considering the information collected and analyzed, we suggest that the structures paraspeckles and histone locus body be incorporated in the TH under the term NB (Table III). These entities are named with the highest percentage in the articles reviewed (Table II) and have the largest amount of

scientific literature describing their functions [17, 18, 30, 48, 49]; on the other hand, the *Gems nuclear body* does not yet have sufficient scientific literature that clearly describes its functions and the Polycomb body is named with a lower percentage in the articles reviewed (Table II). Both structures, the Gems nuclear body and the Polycomb body, should be evaluated in a few more years to identify whether the scientific literature provides further evidence to classify them as NB or not.

One important aspect to emphasize is the lack of uniformity in the nomenclature used for some NB, where according to the author, they are named a certain way, even referring to *Corpusculum convolutum*, in English coiled body, with its eponym Cajal body [6, 7, 21, 43, 50, 55]. Another example is the structure Gems nuclear body, which is also mentioned as Gemini of Cajal bodies or Gemini of coiled body or nuclear gems or Gemini bodies or simply Gems [1, 32, 35, 50], making the bibliographic search associated with this structure difficult. It is worth noting that for the preparation of Table 2 the percentage that appears in the row Gems nuclear body was calculated taking all the aforementioned names into consideration. The main findings indicate that NB *Granulum interchromatineum* (H1.00.01.2.02013), *Macula interchromatinea* (H1.00.01.2.02014), *Corpusculum convolutum* (H1.00.01.2.02015) and *Corpusculum PML* (H1.00.01.2.02011) are listed under the term *Chromatinum* (H1.00.01.2.02004) and not under *Corpusculum nucleare* (H1.00.01.2.02019) in theTH. In this regard, we are attempting, with this initial background, to provide arguments that support the proposal to relocate these terms under the name *Corpusculum nucleare* (Tabla III). In addition, through the analysis of the scientific literature and biological databases, the incorporation of two new entities is suggested in the TH: paraspeckles and histone locus body (Table 3). Gems nuclear body and Polycomb body should be assessed in the near future in the hope of finding greater scientific evidence to support their incorporation in the TH.

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Figure 1. Classification of the nuclear bodies in the *European Bioinformatics Institute* (EMBL-EBI) biological database, *QuickGo* section.

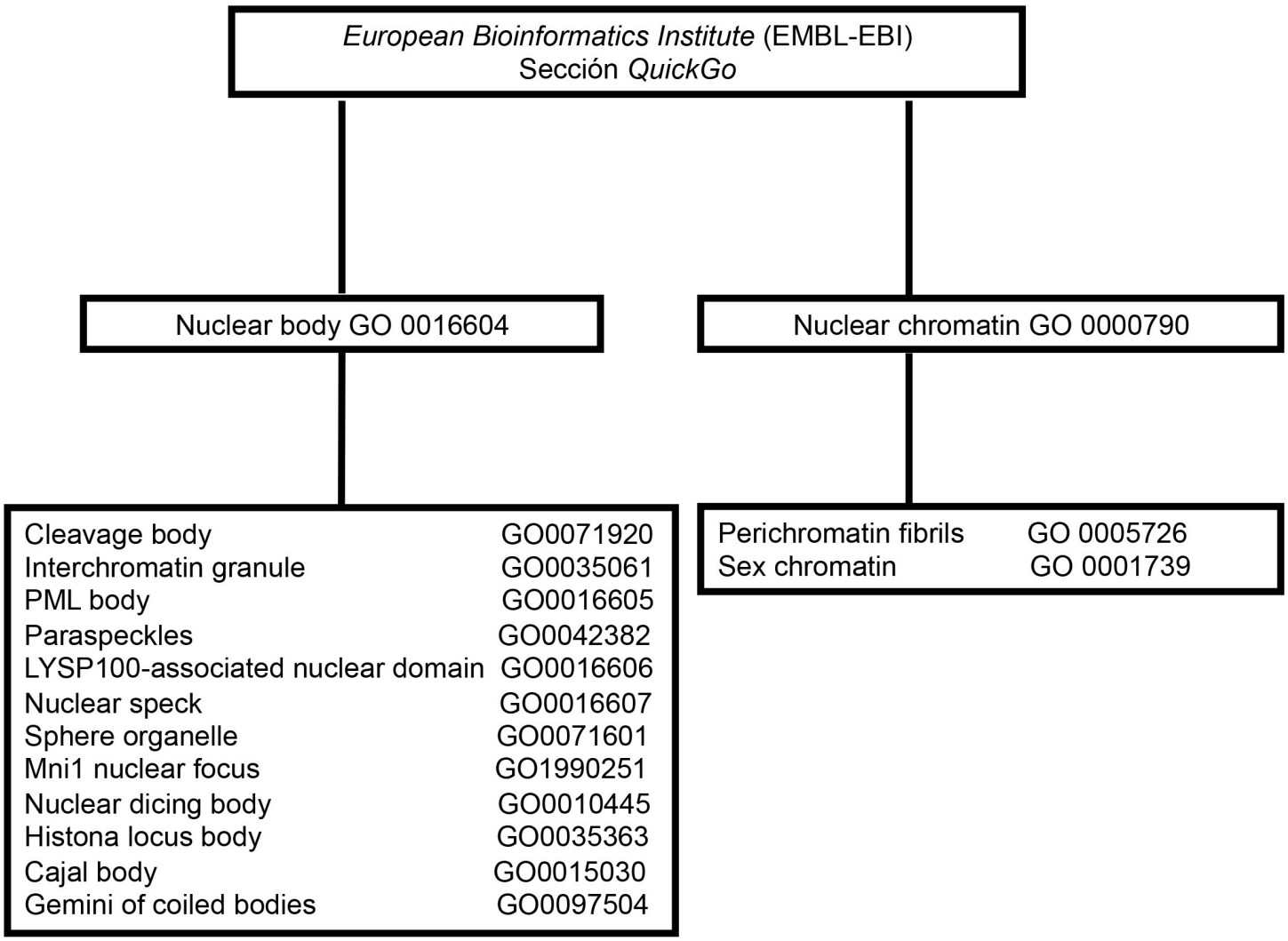
European Bioinformatics Institute (EMBL-EBI)
Sección *QuickGo*
Nuclear body GO 0016604
Nuclear chromatin GO 0000790
Cleavage body GO0071920
Interchromatin granule GO0035061
PML body GO0016605
Paraspeckles GO0042382
LYSP100-associated nuclear domain GO0016606
Nuclear speck GO0016607
Sphere organelle GO0071601
Mni1 nuclear focus GO1990251
Nuclear dicing body GO0010445
Histona locus body GO0035363
Cajal body GO0015030
Gemini of coiled bodies GO0097504
Perichromatin fibrils GO 0005726
Sex chromatin GO 0001739

Table I. Current structure of the *Terminologia Histologica*.

H1.00.01.2.02001	**Nucleoplasma**	**Nucleoplasm; Karyoplasm**
H1.00.01.2.02002	Lamina fibrosa nuclearis	Fibrous lamina; Nuclear lamina
H1.00.01.2.02003	Filamentum lamini	Lamin filament
H1.00.01.2.02004	Chromatinum	Chromatin
H1.00.01.2.02005	Heterochromatinum	Heterochromatin
H1.00.01.2.02006	Euchromatinum	Euchromatin
H1.00.01.2.02007	Fibra chromatini	Chromatin fibre
H1.00.01.2.02008	Fibra nucleosomatis	Nucleosome fibre
H1.00.01.2.02009	Chromatosoma	Chromatosome
H1.00.01.2.02010	Nucleosoma	Nucleosome
H1.00.01.2.02011	Granum nucleosomatis	Nucleosome core particle
H1.00.01.2.02012	Ligamen acid desoxyribonuclearis	DNAlinker
H1.00.01.2.02013	Granulum interchromatineum	Interchromatin granule
H1.00.01.2.02014	Macula interchromatinea	Nuclear speckle; Interchromatin granule cluster
H1.00.01.2.02015	Corpusculum convolutum	Coiled body
H1.00.01.2.02016	Fibrilla perichromatinea	Perichromatin fibril
H1.00.01.2.02017	Corpusculum PML	PML nuclear boby
H1.00.01.2.02018	Chromatinum sexuale	Sex chromatin
H1.00.01.2.02019	Corpusculum nucleare	Nuclear body

Table II. Nuclear bodies. Its shown the percentages in which the different nuclear bodies were mentioned in the selected articles [1, 5, 7, 9, 11, 12, 16, 19, 22, 24, 26, 29, 30, 32, 33, 35, 36, 39, 42, 43, 45, 47, 50, 51, 52, 54].

Nuclear body	Latin name	Percentage in selected articles	Presence in *Terminologia Histologica*
Coiled body	*Corpusculum convolutum*	100.00 %	Yes
Nuclear speckle, Interchromatin granule cluster	*Macula interchromatinea*	96.15 %	Yes
PML nuclear body	*Corpusculum PML*	84.61 %	Yes
Paraspeckles	----	80.76 %	No
Histona locus body	---	57.69 %	No
Gems nuclear body	----	53.84 %	No
Polycomb body	----	50.00 %	No
Stress nuclear body	---	38.46 %	No
Perinuclear compartment (PNC)	---	37.03 %	No
Sam 68 nuclear body	---	23.07 %	No
Cleavage bodies	---	23.07 %	No
Clastosome	---	19.23 %	No
Oct1/PTF/transcription domains	---	19.23 %	No

Table III. Proposal for the reconstruction of the current *Terminologia Histologica*.

H1.00.01.2.02001	**Nucleoplasma**	**Nucleoplasm; Karyoplasm**
H1.00.01.2.02002	Lamina fibrosa nuclearis	Fibrous lamina; Nuclear lamina
H1.00.01.2.02003	Filamentum lamini	Lamin filament
H1.00.01.2.02004	Chromatinum	Chromatin
H1.00.01.2.02005	Heterochromatinum	Heterochromatin
H1.00.01.2.02006	Euchromatinum	Euchromatin
H1.00.01.2.02007	Fibra chromatini	Chromatin fibre
H1.00.01.2.02008	Fibra nucleosomatis	Nucleosome fibre
H1.00.01.2.02009	Chromatosoma	Chromatosome
H1.00.01.2.02010	Nucleosoma	Nucleosome
H1.00.01.2.02011	Granum nucleosomatis	Nucleosome core particle
H1.00.01.2.02012	Ligamen acid desoxyribonuclearis	DNAlinker
----------	Fibrilla perichromatinea	Perichromatin fibril
----------	Chromatinum sexuale	Sex chromatin
----------	Corpusculum nucleare	Nuclear body
----------	Macula interchromatinea	Nuclear speckle; Interchromatin granule cluster
----------	Granulum interchromatineum	Interchromatin granule
----------	Corpusculum convolutum	Coiled body
----------	Corpusculum PML	PML nuclear body
----------		Paraspeckle
----------		Histone locus body