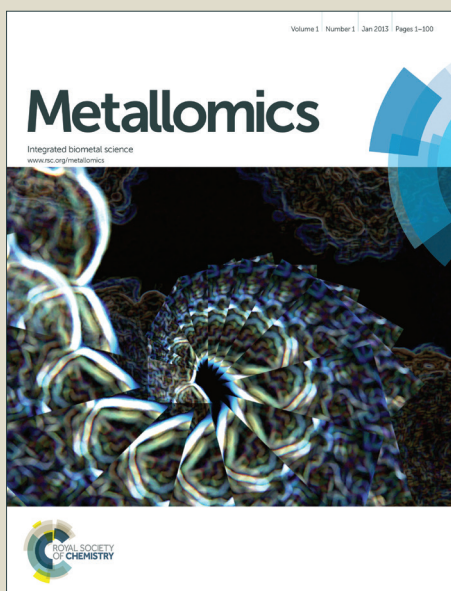


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4 **Serum ferritin is an important inflammatory disease marker, as it is**  
5 **mainly a leakage product from damaged cells**  
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## Abstract

“Serum ferritin” presents a paradox, as the iron storage protein ferritin is not synthesised in serum yet is to be found there. Serum ferritin is also a well known inflammatory marker, but it is unclear whether serum ferritin reflects or causes inflammation, or whether it is involved in an inflammatory cycle. We argue here that serum ferritin arises from damaged cells, and is thus a marker of cellular damage. The protein in serum ferritin is considered benign, but it has lost (i.e. dumped) most of its normal complement of iron which when unliganded is highly toxic. The facts that serum ferritin levels can correlate with both disease and with body iron stores are thus expected on simple chemical kinetic grounds. Serum ferritin levels also correlate with other phenotypic readouts such as erythrocyte morphology. Overall, this systems approach serves to explain a number of apparent paradoxes of serum ferritin, including (i) why it correlates with biomarkers of cell damage, (ii) why it correlates with biomarkers of hydroxyl radical formation (and oxidative stress) and (iii) therefore why it correlates with the presence and/or severity of numerous diseases. This leads to suggestions for how one might exploit the corollaries of the recognition that serum ferritin levels mainly represent a consequence of cell stress and damage.

## Introduction

In mammals (in contrast, for instance, to some functions in insects<sup>1-4</sup>), ferritin is supposed to be a cellular means of storing iron<sup>5</sup>, not of transporting it, yet serum ferritin levels are widely measured as indicators of iron status. However, the soluble transferrin receptor (sTfR):log ferritin ratio (sTfR Index) probably provides a better estimate of body iron over a wide range of normal and depleted iron stores<sup>6-9</sup>. This is because serum ferritin levels can be raised significantly in response to inflammation and/or a variety of diseases (see later). “Serum ferritin” thus presents something of a paradox. Taking a systems approach, we develop and summarise the view that “serum ferritin” actually originates from damaged cells (and thus reflects cellular damage), that it contains some iron but has lost or liberated most of its normal content, and that since the protein part of ferritin is assumed to be benign, that it is this (initially) free iron that correlates with and is causative of disease. The rest of this analytical and synthetic review summarises the wide-ranging evidence for this. We necessarily start by reviewing iron metabolism from a systems point of view.

## A systems biology overview of human iron metabolism

A starting point for systems biology is the creation of the network (mathematically a ‘graph’) of interacting partners (e.g.<sup>10-14</sup>). To this end, a number of recent genomic-level or systems biology reviews have summarised the chief features of human iron metabolism (e.g.<sup>15-19</sup>). (Systems genetics analyses are also available<sup>20-23</sup>.) For the present purposes, aimed at seeking the ‘function’ of human serum ferritin (SF), we shall take a particularly high level view, and assume that the body has a very restricted number of compartments. Fig 2, updated from<sup>15</sup>, shows essentially just three: intestinal tissue, peripheral tissue and blood/serum, and (see also<sup>24,25</sup> and cf.<sup>26</sup>) these will be quite sufficient.

Thus, as is well known, ferric salts and ions are poorly water soluble (hence the need for siderophores – better known in microbiology<sup>27-30</sup>), and much of the complex (redox) chemistry of iron in the body is designed to deal with this. In addition to its existence in divalent and trivalent states, iron is also capable of being liganded in up to 6 places (4 equatorial, 2 polar), and this liganding is necessary to stop its otherwise exceptional reactivity, **specifically the production of the very damaging hydroxyl radical that reacts in nanoseconds with the nearest biological substances**<sup>15, 17</sup> via the Fenton reaction<sup>31-35</sup> of H<sub>2</sub>O<sub>2</sub> and Fe(II). This may be coupled to the re-reduction of Fe(III) to Fe(II) by superoxide in the Haber-Weiss reaction<sup>31-35</sup>, such that unliganded (or poorly liganded) iron moieties are **catalytic** and thus especially dangerous. Thus, while iron is vital for living processes, there is an exceptionally important need to sequester iron in a suitably liganded form, and cellular ferritin is a major means of doing this<sup>36</sup>.

Leaving aside haem, and also nutrient-derived ferritins<sup>37, 38</sup>, iron is absorbed in the intestine as ferrous ions and transported in the serum bound (in the ferric form) to transferrin, where it can enter peripheral tissues via suitable receptors, being re-reduced in the process. Ferrous iron is incorporated into ferritin, simultaneously being oxidised at a di-iron centre<sup>39</sup> to ferric iron. Thus, importantly, ferritin is made in cells (including intestinal cells), and not in serum. We also note the evidence for the presence of ferritin within erythrocytes<sup>40-54</sup>, the largest volume fraction of serum<sup>55</sup>. In nucleated cells, ferritin resides mainly in the cytoplasm, but there are nuclear<sup>56-61</sup> and mitochondrial<sup>62-64</sup> forms (not considered here, as our focus is serum ferritin). An overview of cellular iron metabolism is given in Fig 3.

1  
2 Although there are bacterial (and other) ferritins that have only 12 subunits<sup>65</sup>, human ferritins  
3 consist of 24 subunits of a light (L) and heavy (H) chain arranged by self-assembly in a  
4 tetracosameric, octahedral cage with 4-3-2 symmetry (e.g.<sup>5,66-70</sup>). In humans, the molecular masses  
5 of the two chains are 19 (173 amino acids) and 21 kDa (183 amino acids), respectively<sup>61</sup>, and the  
6 subunits are structurally interchangeable<sup>71</sup>, even between mammalian species<sup>72</sup>. The heavy subunit  
7 is primarily responsible for the ferroxidase activity of the ferritin complex<sup>39</sup>, whereas the light  
8 subunit (L also standing for Lacks catalysis<sup>73</sup>) facilitates the storage of iron into the ferritin core<sup>61</sup>.  
9 Many X-ray structures are known<sup>74</sup>. Broadly, each subunit consists of a 4-helix bundle, and their  
10 self-assembly (whether iron is present or not) is energetically extremely favourable – the melting or  
11 denaturation temperature of the 24mer cage is some 40°C greater than that of an individual subunit  
12  
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14  
15

### 16 Iron loading mechanism of ferritin

17 The main features of the typical 24-subunit ferritin architecture (shown as an all-H-chain variant)  
18 are given in Fig 4. Human ferritin is some 12-nm diameter overall, with a 2nm thick protein shell  
19 and a hollow internal 8-nm diameter cavity capable of holding up to 4500 iron atoms. Ferrous ions  
20 can diffuse into (and out of) the core via the eight, hydrophilic ~4Å x 15-20Å channels located at  
21 the 3-fold symmetry axis<sup>70, 73, 76-82</sup>, where they are oxidised by dioxygen (or H<sub>2</sub>O<sub>2</sub> if present) at a  
22 di-iron catalytic site to form Fe(III)<sub>2</sub>-O products that then form the Fe<sub>2</sub>O<sub>3</sub>·H<sub>2</sub>O mineral core<sup>78, 83, 84</sup>.  
23 Other materials such as phosphate may also serve as counterions<sup>82, 85</sup>. Ferritin Fe<sup>3+</sup>O nucleation  
24 channels open onto the internal surfaces of ferritin protein cages at the four-fold symmetry axes of  
25 the ferritin protein cage<sup>82</sup>. The six channels located at the 4-fold axis of the protein are  
26 hydrophobic; their function does not seem to be known with any certainty, but they may permit  
27 entry of dioxygen and/or H<sub>2</sub>O<sub>2</sub><sup>77</sup>.  
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33 It is not quite so clear how (after storage as Fe (III) in the ferritin core) Fe(II) exits the channels<sup>81, 86</sup>  
34 to become available to cells, nor how the physiological (*in vivo*) reductant reaches the potential site  
35 of reduction inside the small channels. It is not clear even what the physiological reductant is<sup>87</sup>,  
36 though NADH and FMN have been reported to serve<sup>82, 88</sup>, as have superoxide<sup>89</sup> and other materials<sup>81</sup>.  
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### 40 How much iron in cellular/tissue ferritin?

41 The number of iron atoms/ferritin cage is said to average 1000–1500 normally<sup>73</sup>, governed more by  
42 iron availability than anything else, with a maximum of 4500 iron atoms normally being quoted  
43 (e.g.<sup>90-92</sup>, and attained for iron overload conditions or when loaded artificially *in vitro*). Direct  
44 observation also leads to a mode value of ~1500 in a liver biopsy from a patient with hereditary  
45 haemochromatosis<sup>93</sup>.  
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48

### 49 What kind of ferritin in which tissues?

50 As mentioned, from a structural point of view in terms of forming the 24mer nanocage, ferritin H  
51 and L forms are interchangeable<sup>71</sup>. Similarly, as expected, ferritin is expressed in most tissues.  
52 Thus, human protein atlas expression data for the light chain  
53 <http://www.proteinatlas.org/ENSG00000087086/normal> show it mainly in CNS, bone marrow,  
54 spleen, liver, kidney, lung and adipocytes. Expression of the heavy chain is broadly similar  
55 <http://www.proteinatlas.org/ENSG00000167996/normal> save that it is also highly expressed in  
56 breast, uterus, testis, prostate and thyroid tissue. In terms of the actual stoichiometries of L:H in  
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ferritin molecules in different tissues (which also affects the ordering or crystallinity of the mineral core<sup>73, 87</sup>) there is rather less information, and variations in this may be causative of disease<sup>94, 95</sup>. Clearly, For a 24-subunit molecule with two kinds of subunits, one can build 25 canonical ‘isoferritins’<sup>74</sup>. Liver and spleen ferritin is mainly the L subunit while heart and brain ferritin is mainly the H subunit. Serum ferritin is mainly in the L form<sup>5, 96</sup>, consistent with the view that it typically originates in the liver<sup>97</sup>. The same is presumably true for erythrocyte ferritin, in that this is what the usual ELISA tests for serum ferritin are designed to detect.

### Natural degradation of ferritin

The exact circumstances under which ferritin is normally degraded *in vivo* (if it is intact) are not entirely clear, but what is clear is that there is a fundamental conceptual problem, in that if the only part degraded is the protein the result is the damaging liberation of unliganded iron. Certainly, as expected for normal cellular degradation, the proteasome is involved<sup>38, 98</sup>, but there is also a major lysosomal degradation pathway<sup>38, 99-103</sup>. We note too that overexpression can lead to the formation of ferritin inclusion bodies<sup>104</sup>.

As well as proteolytic degradation, there are other means of ferritin removal. Thus, haemosiderin is an insoluble material formed from damaged ferritin (ferritin with exposed and potentially chemically reactive mineral sites), commonly appearing under conditions of iron overload and often reflecting a poorer disease prognosis (e.g.<sup>71, 105-112</sup>). (Note that another insoluble cellular degradation cluster – lipofuscin (e.g.<sup>113-116</sup>) – is different, as it does not contain haemosiderin. However, the insoluble substance neuromelanin (e.g.<sup>115, 117-119</sup>) may contain ferritin or ferritin-like material<sup>120-122</sup>. The question of what happens to haemosiderin seems rather poorly understood, but in contrast to ferritin it is not normally seen (nor at least measured) in serum<sup>123, 124</sup>; since it is composed of large, insoluble aggregates it is possibly not surprising that it does not leak from cells. Overall, however, it seems that we have comparatively little information on the important question of what happens to its iron content when the protein part of the ferritin molecule either leaves the intracellular environment or is degraded.

**In what form is serum ferritin measured?** As mentioned previously, ferritin has an H and L form that are structurally interchangeable. Serum (L-)ferritin is usually measured with antibodies; only rarely is its iron content measured as well. Mass spectrometric methods, that can measure both protein and internal materials, may thus be expected to become the methods of choice<sup>125-128</sup>. When such measurements are done, serum ferritin is usually found to contain some iron, but nothing like its full complement<sup>91, 92, 97, 129, 130</sup>. This implies that it has lost it, whether during or after effluxing from the cells in which it originates<sup>87</sup>.

### Is the protein component of serum ferritin benign or toxic?

This question arises because if the iron has escaped and now (say) the inside of the ferritin is exposed in the serum it might have effects that the intact protein does not (given that the intact protein is extremely stable to thermal unfolding<sup>75</sup>). There is some fragmentary evidence that serum ferritin itself may have apoptotic and other actions on cells<sup>68, 131, 132</sup>. However, at present it is rather difficult to answer the question of how benign the **protein-only** form of ferritin (i.e. apoferritin) actually is, since serum ferritin does always tend to contain at least some iron, which can be released and is then not at all benign. When the iron is varied systematically, it is iron-loaded ferritin that is the more toxic<sup>133</sup>, with apoferritin in fact being protective<sup>133-137</sup>. An important piece

of evidence comes from the fact that homozygous ferritin knockout mice are embryo-lethal<sup>138</sup> but that heterozygous *Fth*<sup>+/-</sup> mice are fairly normal save that they have greatly increased levels of serum ferritin but unchanged serum iron<sup>139</sup>. This shows us, importantly, (i) that iron and ferritin can be regulated independently, and (ii) that excess ferritin protein is not of itself toxic *in vivo* (see also<sup>140</sup>). Hereditary hyperferritinemia-cataract syndrome is another disease in which serum ferritin is high but there is no evidence of systemic iron overload<sup>141-146</sup>. However, as well as (sometimes) being a marker of liver iron stores, serum ferritin is also an inflammatory marker, and there is often a considerable correlation between disease status and the serum ferritin protein level as measured using antibodies (which do not distinguish ferritins with varying iron content).

### Serum ferritin can be a marker of iron stores but is also an inflammatory biomarker

What matters from the point of view of mammalian biology is both the total amount of iron and its speciation. While iron is necessary in every metabolising tissue, a substantial amount of iron is held in the liver, so ‘liver iron stores’ are often taken as the gold standard. Traditionally, these were measured in a biopsy, although this is not something that can be done with any frequency. Fortunately non-invasive measurement and imaging methods, e.g. neutron-stimulated emission controlled tomography<sup>147</sup>, SQUID-biosusceptometry<sup>129, 148</sup> and (in particular) MRI (e.g.<sup>149-158</sup>), also widely used for brain imaging (e.g.<sup>159-161</sup>), are coming through. In some cases, where there is no inflammation and/or if a specific iron-related disease state is known, liver iron content can correlate with serum ferritin (e.g.<sup>162, 163</sup>), but more often the correlation is poor (e.g.<sup>129, 157, 164-171</sup>). This is more or less inevitable when serum ferritin levels can be affected by two largely independent causes, viz iron status and inflammatory status. Thus, as mentioned above, serum ferritin alone is falling out of favour as a marker of iron status, with serum (‘soluble’) transferrin receptor (sTfR) being seen as much more useful, since sTfR may be used to distinguish the anaemia of chronic disease from iron-deficiency anaemia<sup>172</sup>. In particular, the “sTfR Index” (the sTfR/log ferritin ratio when both are measured in  $\mu\text{g.L}^{-1}$ ) is now considered to provide an estimate of body iron over a wide range of normal and depleted iron stores<sup>6-9</sup>, and again is thus better for discriminating iron deficiency anaemia from the anaemia of chronic disease<sup>9, 173-175</sup> (cf.<sup>176</sup>).

In consequence, and especially in countries where inflammatory diseases are highly prevalent, it would seem that serum ferritin may in general be a better marker of inflammation than of iron status.

### Some diseases in which serum ferritin levels correlate with the presence or severity of disease

One of us has previously listed a great many (inflammatory) diseases in which iron dysregulation clearly plays a major role (e.g.<sup>15, 17</sup>), but did not there distinguish serum ferritin explicitly. It is therefore helpful to set down some of the studies in which serum ferritin is known to associate with disease and/or disease severity, and this is done in Table 1.

Table 1. A selection of diseases in which their presence or severity is known to be related to serum ferritin levels. The Table purposely excludes classic ‘iron overload’ diseases such as haemochromatosis, thalassaemia and myelodysplastic syndrome. It also excludes syndromes such as Alzheimer’s disease<sup>177-179</sup> and Parkinson’s disease<sup>18, 180</sup>, where a great many papers show



dysregulation of iron metabolism in brain tissue but where there is very little work in serum. In the case of rheumatoid arthritis some of the studies involved synovial fluid; like serum, this is an extracellular fluid.

<b>Disease or syndrome</b>	<b>Selected references</b>
Acute respiratory distress syndrome	181-184
Amyotrophic lateral sclerosis	185-189
Atherosclerosis	96, 190-200
Cancer	201-214
Cirrhosis of the liver	215-217
Coronary artery disease	218-221
Diabetes mellitus, type 2	221-249
Hypertension	250-254
Metabolic syndrome	235, 236, 252, 255-272
Multiple sclerosis	273-276
Myocardial infarction	277-285
Non-alcoholic fatty liver disease	260, 262, 264, 270, 286-301
Preeclampsia	302-306
Rheumatoid arthritis	307-314
Sepsis/ SIRS	315-318
Stroke	319-330
Systemic lupus erythematosus	274, 331-342

There can be very little doubt that high serum ferritin levels accompany a great many diseases, and the corollary of this is that iron-induced hydroxyl radical formation leading to oxidative damage is likely to be a contributory factor in all of them. In addition, there are other useful phenotypic readouts that change with serum ferritin, and the next section describes one.

## Some morphological and related readouts of haematological changes associated with inflammatory diseases

While not the entire focus of this review, there are two other accompaniments to the unliganded iron caused by its loss from ferritin, namely morphological changes to both fibrin and erythrocytes. Thus, we have recently been developing the idea that many of the consequences of unliganded iron can be observed directly, by changes in properties such as erythrocyte (RBC) morphology and deformability and the nature and morphology of fibrin fibres generated in the presence of thrombin (as is observed in a number of diseases<sup>343-346</sup>). When thrombin is added to healthy whole blood, the RBCs will keep their typical discoid shape while fibrin fibres will form over and around the RBCs (such a typical healthy RBC (from an individual with a serum ferritin of 19 ng.mL<sup>-1</sup>), surrounded by fibrin is shown in Fig 5A). However, in inflammatory conditions, where iron overload is present, the RBCs lose their typical discoid shape, while the fibrin network forms a dense matted layer. This was previously noted in RBCs of hereditary haemochromatosis, pro-thrombin mutation and antiphospholipid syndrome with increased serum ferritin levels and in high serum ferritin levels in Alzheimer's disease<sup>347-351</sup>. Figs 5 B-D show examples of RBCs and fibrin in these conditions. The corollary is clear, namely that these kinds of changes should be observable in cases where we see high serum ferritin, and some examples have already been published.

In the presence of iron, the already compromised RBCs are entrapped in the pathological fibrin masses. Iron plays an important role in the change of a netlike fibrin layer to a matted mass. We previously showed that healthy fibrin can be changed to resemble this matted appearance, when physiological levels of iron is added to plasma<sup>352</sup>. Such matted fibrin morphology was also previously noted in type II diabetes, thrombotic ischemic stroke and systemic lupus erythematosus. Here the compromised RBCs twist around the fibres and this may cause a tight and rigid clot that might be particularly resistant to fibrinolysis<sup>353-355</sup>.

As well as undergoing a shape change, the RBC membranes, in the presence of iron overload, also lose their elastic ability (deformability). This was noted in Alzheimer's Disease individuals with iron overload, where their RBCs have a decreased membrane elasticity<sup>347</sup>. A changed RBC membrane roughness was also noted in diabetes<sup>356</sup>.

Further, RBC shape and membrane changes have been noted in smokers and individuals with Chronic Obstructive Pulmonary Disorder (COPD)<sup>357, 358</sup>. Both conditions are known to cause a general inflammatory state in the user as well as increased serum ferritin levels<sup>359</sup>, and this may aid in the developing of the changed RBC deformability.

RBCs are extremely adaptable cells, particularly due to their rheological properties that force them to deform and reform under shear forces when they travel through narrow capillaries, while in the presence of high (poorly liganded) iron levels, they lose this deformability. By contrast, diseased RBCs can regain their discoid shape when selected chelators are added<sup>350</sup>. Here we show how an RBC from a HH individual can return to the typical discoid shape after the addition of physiological levels of the iron chelator Desferal (Fig 5E and F). This may have profound clinical implications under conditions where iron overload is present.

Thus, this unliganded iron affects (negatively) at least three things that can each contribute to vascular woes: erythrocyte morphology, erythrocyte deformability and fibrin structure/morphology.

## Chelation for the reversal of iron-induced effects

The recognition that these changes can be reversed by known iron chelators leads to the recognition of a further prediction: that disease severity may be decreased through the use of iron chelators that may be pharmacological or nutritional. For the former, three iron chelators have been approved for clinical use (e.g. <sup>15, 360-364</sup>), viz desferal/ deferoxamine/ desferrioxamine <sup>365</sup>, L1/ deferiprone <sup>366-368</sup> and deferasirox <sup>369-372</sup>. From the nutritional point of view, there is considerable evidence that many of the benefits of polyphenolic antioxidants (such as are found in coloured, and especially purple, fruits) derive from their ability to chelate unliganded iron (see e.g. <sup>17, 373-380</sup>).

## Chemical kinetic basis of the relation of serum ferritin to liver iron stores and with disease

Many dozens of references indicate that in normal humans (without overt inflammation) serum ferritin levels are more or less closely related to body iron stores (e.g. in the liver) as judged by magnetic resonance imaging, biopsy or repeated phlebotomies. A selection of such references includes <sup>163, 169, 381-385</sup>.

Since there is normally a decent correlation between body iron stores and serum ferritin, a series of simple (even first order) reactions in which cells release ferritin can account for this (Fig 6). The question arises as to the nature of this ‘release’.

## Ferritin transfer from cells to serum in humans: less active secretion, more simply leakage from damaged cells

Partly because a fraction of serum ferritin is glycosylated, as judged more or less solely by its ability to bind to concanavalin A (not a very specific assay), it is occasionally stated that ferritin is ‘secreted’ (e.g. <sup>382, 386, 387</sup>), implying a controlled process, but without – so far as we are aware – any actual evidence for secretion rather than leakage being the mechanism *in vivo*. Indeed when ferritin is genuinely secreted, as it is for instance in insects <sup>3, 4, 388</sup>, it has suitable leader (secretion signal) sequences, and mammalian ferritins do not.

This said, in cell cultures, there is some (scant) evidence for a comparatively small amount of regulated secretion <sup>389</sup>, and one paper states that secretion can be decreased by brefeldin, an inhibitor of Golgi processes <sup>390</sup>. This secreted form is said to be mainly the more acidic H form <sup>131</sup> and is glycosylated. We note that both SCARA5 and the transferrin receptor can act as receptors for serum ferritin <sup>68, 391, 392</sup>, as can TIM-2 in mice <sup>393</sup>, that can in some circumstances be taken up into cells <sup>394</sup>. There is also evidence for active secretion (of a non-glycosylated form) in mice <sup>395</sup>. Overall, however, there is not as yet any real evidence for regulated or active secretion in humans *in vivo*, such that the origin of serum ferritin must indeed largely, if not entirely, be seen as cellular damage. A number of analyses in the literature are consistent with this, and the following four sections pertain.

## Relative lack of homeostasis of serum ferritin

The ‘normal range’ of a biochemical concentration in a body fluid is usually taken as the middle 95 percentiles. Somewhat like the Gini indices of economics <sup>396</sup>, it is then possible to assess the ratio of particular percentiles, which gives an indication of the spread of these among populations. We shall call this this ratio (of the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentile) the 95 percentile ratio or 95PR. A small spread implies a tighter degree of regulation or control. The large normal range of serum ferritin (18-350

ng.mL<sup>-1</sup>) relative to other biochemical variables ([http://www.globalrph.com/labs\\_def.htm#Ferritin](http://www.globalrph.com/labs_def.htm#Ferritin)), with a 95PR of nearly 20, implies that it is not the subject of homeostasis, i.e. that its appearance is not regulated. One might also comment on the very low normal concentrations of serum ferritin (up to say 350 ng.mL<sup>-1</sup> in men, up to say 150 ng.mL<sup>-1</sup> in women) relative to say transferrin (1.88-3.41 mg.mL<sup>-1</sup>) ([http://www.globalrph.com/labs\\_t.htm](http://www.globalrph.com/labs_t.htm)) or fibrinogen (2-4 mg.mL<sup>-1</sup>).

### Association between serum ferritin and biomarkers of liver damage

As stated by Theil<sup>70</sup>: “serum ferritin likely originates from cell leakage”. The figure in<sup>67</sup> implies a similar role. Similarly, Hubel<sup>305</sup> points out correlations between serum aspartate aminotransferase (a marker of hepatocellular damage) and SF<sup>397</sup>, which again implies that serum ferritin originates from cellular damage. Many other authors (e.g.<sup>87, 91, 129, 288, 382, 398</sup>) take a similar view. Serum alanine aminotransferase is another well known marker of liver damage that correlates with serum ferritin<sup>93, 215, 257, 287-289, 399-407</sup>, consistent with the view that serum ferritin is indeed a marker of damaged cells. In this regard, it is worth noting that the rate of cell turnover, and especially liver cell turnover/regeneration, can be very high (e.g.<sup>408-411</sup>).

### Correlation of serum ferritin with other markers of oxidative stress and hydroxyl radical formation

Since intracellular ferritin is a means of storing iron safely<sup>412</sup>, and indeed its synthesis is increased in response to oxidative stress<sup>413-416</sup>, one should not expect serum ferritin to be related to biomarkers reflecting hydroxyl radical formation via the Fenton reaction, that is catalysed by unliganded iron. However, in a similar vein to the liver damage above, serum ferritin levels do correlate with serum markers of hydroxyl radical formation such as 8-hydroxydeoxyguanosine<sup>17, 417-424</sup>, 27-hydroxycholesterol<sup>425</sup>, 4-hydroxynonenal<sup>131, 290</sup>, isoprostanes<sup>426, 427</sup>, and malondialdehyde<sup>406, 428-436</sup>. Given that only unliganded iron can do this, the easiest interpretation of such data is that the serum ferritin has lost its iron and that it is this unliganded iron that catalyses hydroxyl radical formation and thus the production of these markers. An extensive food processing literature also documents this loss of iron from ferritin in muscle foods (e.g.<sup>437-439</sup>), where the consequent lipid oxidation is a major issue in causing rancid tastes, and where metal chelators decrease it<sup>440, 441</sup>.

### Correlation of platelet microparticles with serum ferritin – further evidence for the cell damage hypothesis

As mentioned, a considerable number of papers note the presence of ferritin in erythrocytes, the largest cellular compartment in blood<sup>40, 43-50, 53, 54</sup>. In RBCs, one of the more notable cell death mechanisms is eryptosis, a suicidal death of erythrocytes; this is characterized by erythrocyte shrinkage, blebbing, and phospholipid scrambling of the cell membrane. There is limited evidence that eryptosis occurs in iron overload conditions like  $\beta$ -thalassemia<sup>442</sup>. It is noteworthy that erythrocyte-derived microparticles are also often observable in the blood of patients with diseases associated with high serum ferritin levels (Table 1)<sup>443-453</sup>. These microparticles are circulating fragments derived from blebbing and shedding of cell membranes through several mechanisms that include activation, apoptosis (in nucleated cells) and cell damage<sup>444, 454</sup>. These microparticles are well-known in cardiovascular, neoplastic, and inflammatory diseases and this again implies a correlation between cellular damage and serum ferritin. Cell damage also releases both

1  
2 phospholipids and DNA, and (in a similar vein) ferritin levels are also raised in diseases in which  
3 antibodies to such molecules are also present (e.g. <sup>455-457</sup>).

### 4 5 **Summarising remarks**

6 Although serum ferritin is widely seen as an inflammatory biomarker, our understanding of its role  
7 as an intracellular iron storage protein gives no explanation of why it should even exist in serum.  
8 The view summarised here is that serum ferritin leaks from damaged cells, losing most of its iron on  
9 the way, and leaving that iron in an unliganded form that can impact negatively on health. This  
10 unliganded iron can of course stimulate further cell damage <sup>17</sup>. This overall view serves  
11 straightforwardly to explain the following, known observations.  
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- 14 1. Serum ferritin exists, despite the fact that ferritin is not synthesised in the serum
- 15 2. Serum ferritin lacks most of the iron it contained when intracellular
- 16 3. The intracellular ferritin must have ‘dumped’ its unliganded iron somewhere, where it can  
17 participate in Haber-Weiss and Fenton reactions, creating hydroxyl radicals and consequent  
18 further cellular damage.
- 19 4. The serum ferritin protein is itself considered benign <sup>139</sup>
- 20 5. Yet the level of serum ferritin correlates with numerous inflammatory and degenerative  
21 diseases  
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### 26 **Quo vadis (where next)? A perspective for future work**

27 We consider the summary presented here rather persuasive, as it has considerable explanatory  
28 power in terms of accounting for the nature and consequences of serum ferritin, and providing  
29 corollaries of the fact that it has largely ‘lost’ its iron that are borne out by evidence. It also leads us  
30 to note some of the experiments that need to be done. First, we need to understand much better the  
31 state of both cellular and serum ferritin in terms both of its subunit composition and the nature and  
32 extent of its iron content. We also need to understand better the different cellular and tissue  
33 distributions of the variously loaded forms, and we certainly need to determine the toxicity  
34 displayed, or protection afforded, by the different forms of well characterised ferritins under  
35 different circumstances. Far from implying that serum ferritin is a poor biomarker, it leads us rather  
36 to suggest that we need to follow it (and its sequelae) more carefully and longitudinally during the  
37 development or otherwise of various diseases, and to test how well its changes reflect therapeutic  
38 benefits to disease progression. Only then will we determine its true utility, whether alone or in  
39 combination with other biomarkers.  
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### 46 **Acknowledgments**

47 We thank Dr Steve O’Hagan for considerable assistance with a number of the figures.  
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## Legends to Figures

Fig 1. An overview of this manuscript. **A.** A Mind map representation; to read this start at “1 o’clock” and go clockwise. **B.** A representation as an infographic, covering (0) the systems biology of iron metabolism, (1) the nature and structure of serum ferritin (SF), (2) the relationship between SF and body iron stores and its measurement, the relationship between SF and (3) markers of oxidative stress and (4) disease, and finally (5) the evidence that ferritin is transferred from cells to serum mainly via cell damage and leakage rather than by regulated secretion.

Fig 2. A high-level, three-compartment overview of iron metabolism (based on <sup>15</sup>) and the means by which we consider that ferritin appears in serum by leakage from peripheral (and possibly intestinal) cells. BR biliverdin reductase, DMT1 divalent metal transporter1, HO haem oxygenase, Hph hephaestin, TfR transferrin receptor, Lcn2 lipocalin2, also known as Neutrophil gelatinase-associated lipocalin. Diagrams rendered by Dr Steve O’Hagan.

Fig 3. Some relevant aspects of cellular iron metabolism, including ferritin as its possible loss to serum. The figure is not to scale, and is based in part on <sup>67</sup>. Membrane protein concentrations shown are lower (for clarity) than those in real cell membranes <sup>458</sup>. Diagrams rendered by Dr Steve O’Hagan.

Fig 4 The architecture of a human ferritin, rendered from PDB structure 1FHA (all-H-chain variant). **A.** A view down one of the hydrophilic channels representing the 3-fold axis of symmetry through which iron enters the ferroxidase site en route to the core. **B.** A view down the hydrophobic channels representing the 4-fold axis of symmetry (whose function is unknown). **C.** Entry of Fe<sup>2+</sup> into ferritin via a hydrophilic channel, and conversion at a di-iron site to Fe<sup>3+</sup>, based loosely on a diagram in <sup>73</sup> – note that for clarity the iron atoms not drawn to scale. Diagrams rendered by Dr Steve O’Hagan.

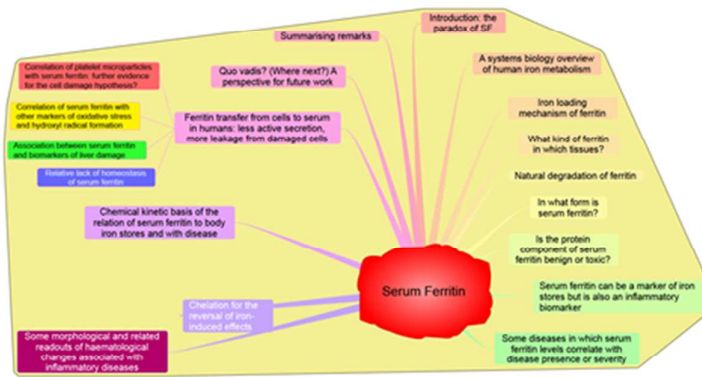
Fig 5. **5A to D:** Whole blood with added thrombin, taken from females. **A)** Erythrocyte surrounded by fibrin network, from a healthy individual (serum ferritin (SF) = 19 ng/mL); **B)** Erythrocyte from a hereditary hemochromatosis individual (C282Y/C282Y) showing elongated shape with (in brown) matted fibrin (serum ferritin (SF) = 506 ng.mL<sup>-1</sup>); **C)** Erythrocyte of an individual with a pro-thrombin mutation (G20210A - heterozygous) as well as anti-phospholipid syndrome, showing fibrin forming a covering on the elongated erythrocyte (serum ferritin (SF) = 177 ng.mL<sup>-1</sup>); **D)** Erythrocyte from a high serum ferritin Alzheimer’s disease individual, showing architectural changes of the cell (serum ferritin (SF) = 256 ng.mL<sup>-1</sup>). **5E and F:** Whole blood smears (without added thrombin) **E)** Erythrocyte of hereditary individual (serum ferritin (SF) = 506 ng.mL<sup>-1</sup>); **F)** Erythrocyte from hereditary hemochromatosis individual after addition of the iron chelator desferal (167 μM). Scale bar = 1 μm.

Fig 6. A high-level systems approach to serum ferritin. The diagram serves to illustrate why there tend to be correlations between the amount of ferritin in cells, the rate of its excretion by cell damage (involving liberation of unliganded iron) and the levels of serum ferritin. The serum ferritin correlates with disease but the cause is iron, with which it too can correlate. As with any systems biology network, multiple differences in different elements of the network can lead to the same overall effects, explaining the lack of a perfect correlation with any individual process. Thus a first order rate of efflux of ferritin is the product of (and thus contains contributions from) both the

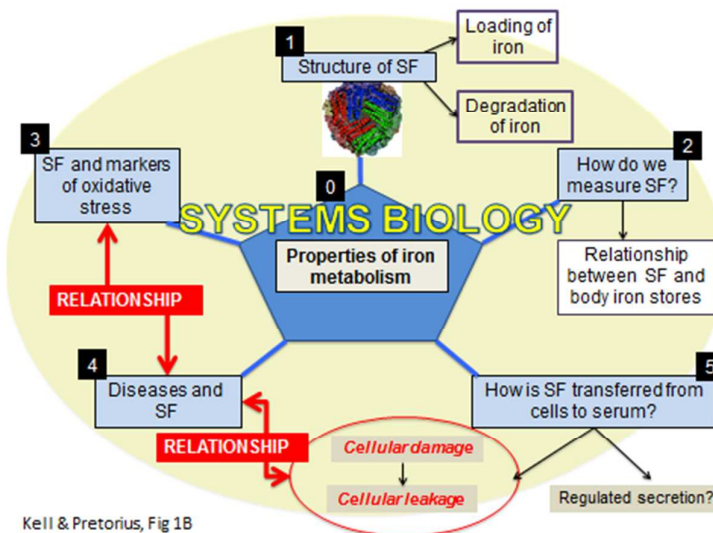
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2 internal ferritin concentration and the rate constant for efflux, which may vary independently. For  
3 these purposes we do not discriminate the many individual iron species.  
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Figures

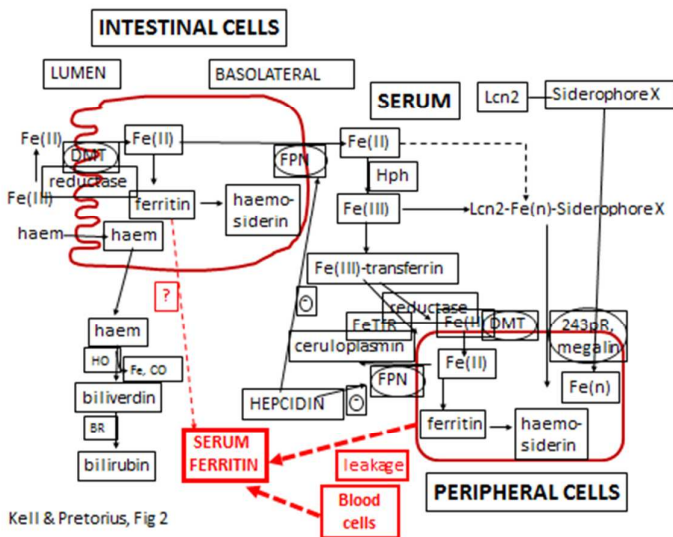
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Kell & Pretorius, Fig 1A

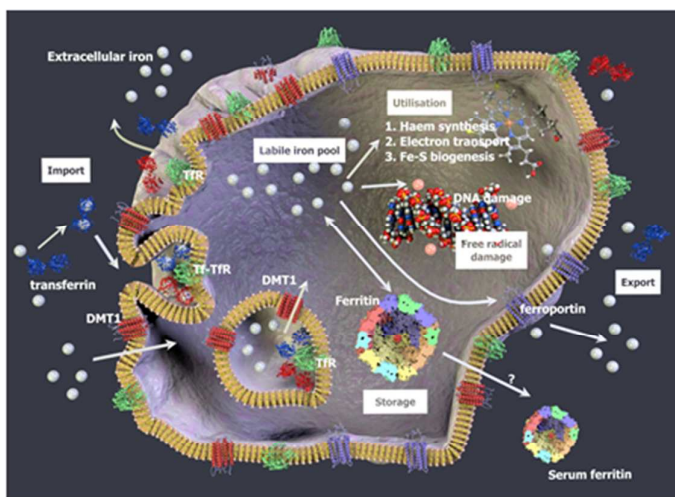


Kell & Pretorius, Fig 1B

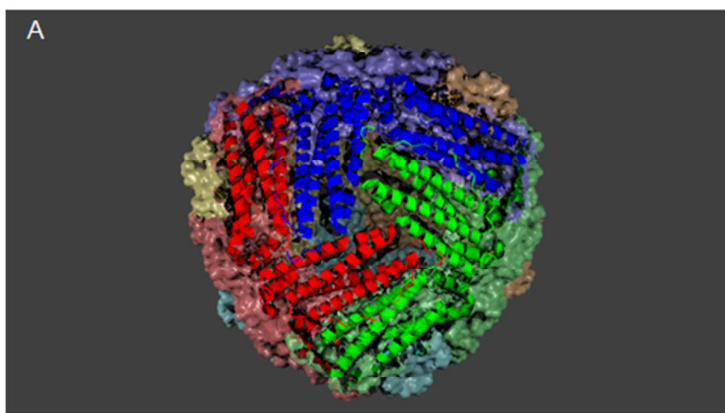


Kell & Pretorius, Fig 2

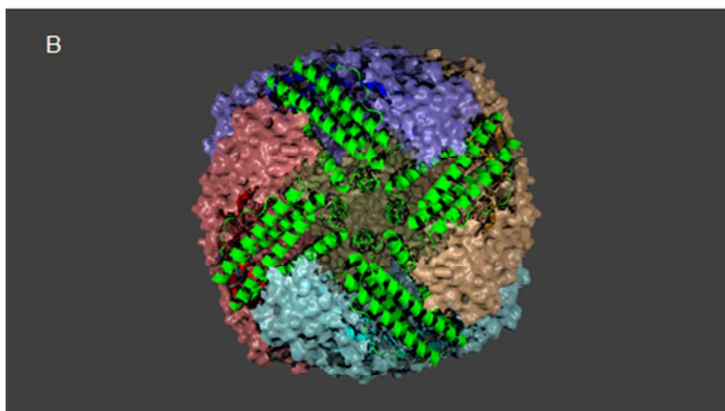




Kell & Pretorius, Fig 3



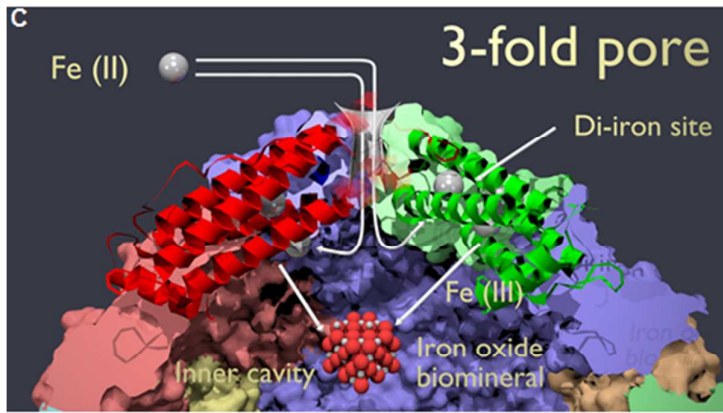
Kell & Pretorius, Fig 4A



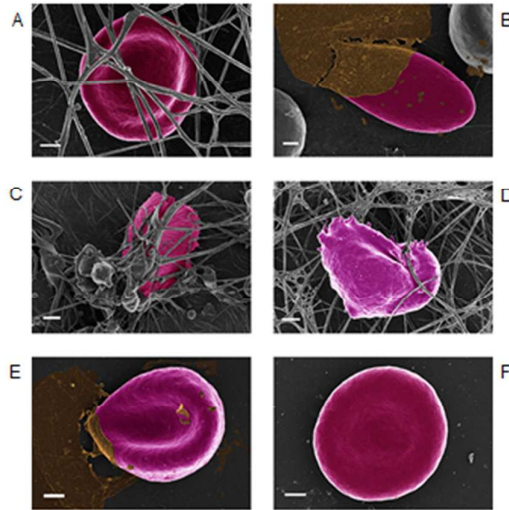
Kell & Pretorius, Fig 4B

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### Iron uptake by ferritin

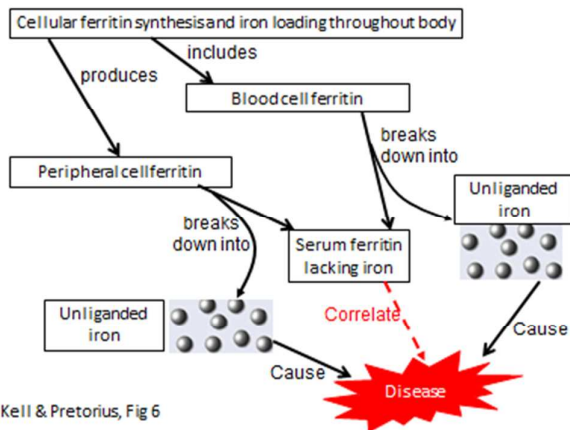


Kell & Pretorius, Fig 4C



Kell & Pretorius, Fig 5

### A high-level systems approach to serum ferritin



Kell & Pretorius, Fig 6

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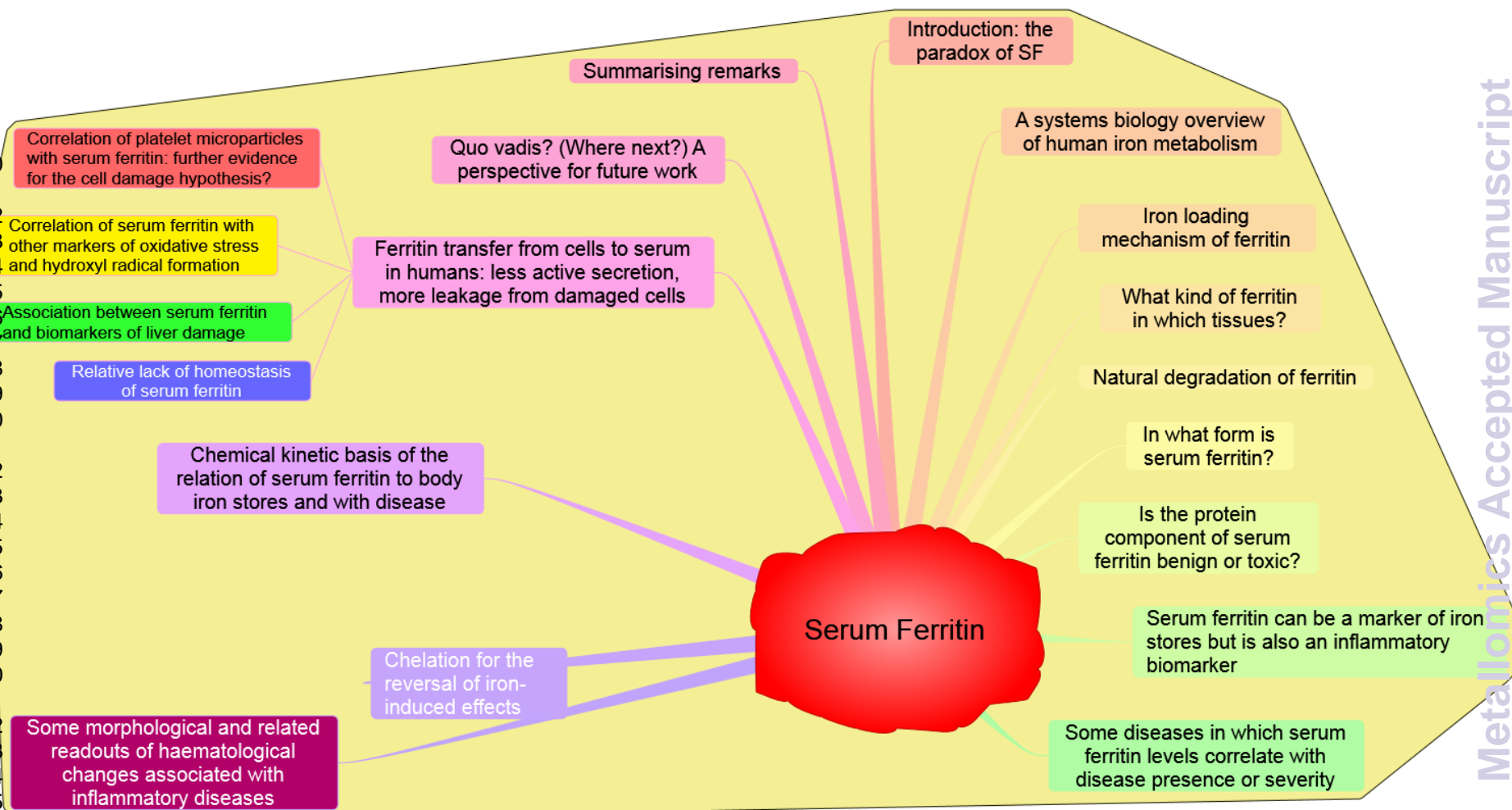
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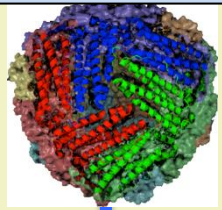
Kell & Pretorius, Fig 1A

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Metallomics

1

Structure of SF



Loading of iron

Degradation of iron

2

How do we measure SF?

Relationship between SF and body iron stores

3

SF and markers of oxidative stress

# SYSTEMS BIOLOGY

0

Properties of iron metabolism

**RELATIONSHIP**

4

Diseases and SF

**RELATIONSHIP**

How is SF transferred from cells to serum?

*Cellular damage*

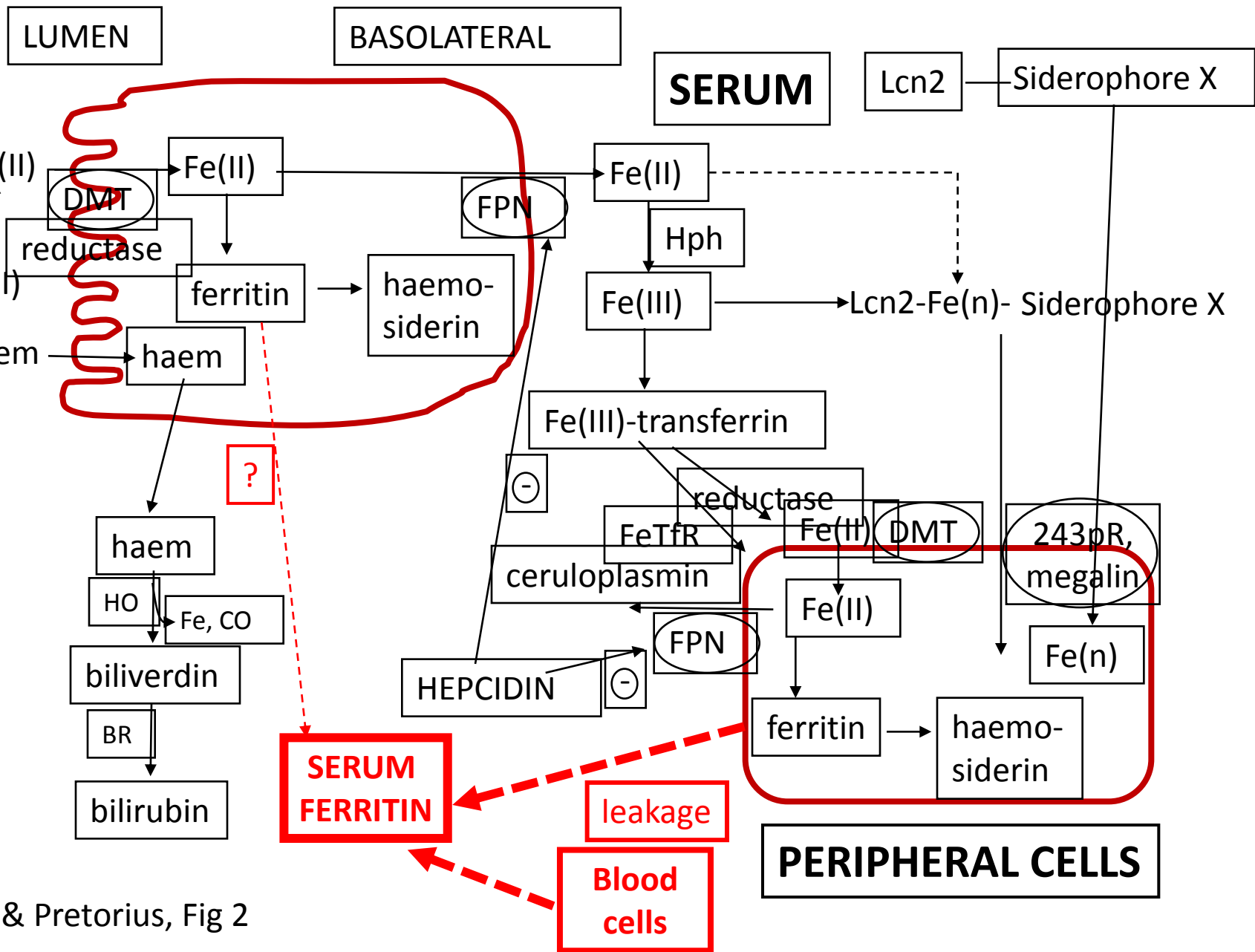
*Cellular leakage*

Regulated secretion?

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**INTESTINAL CELLS**

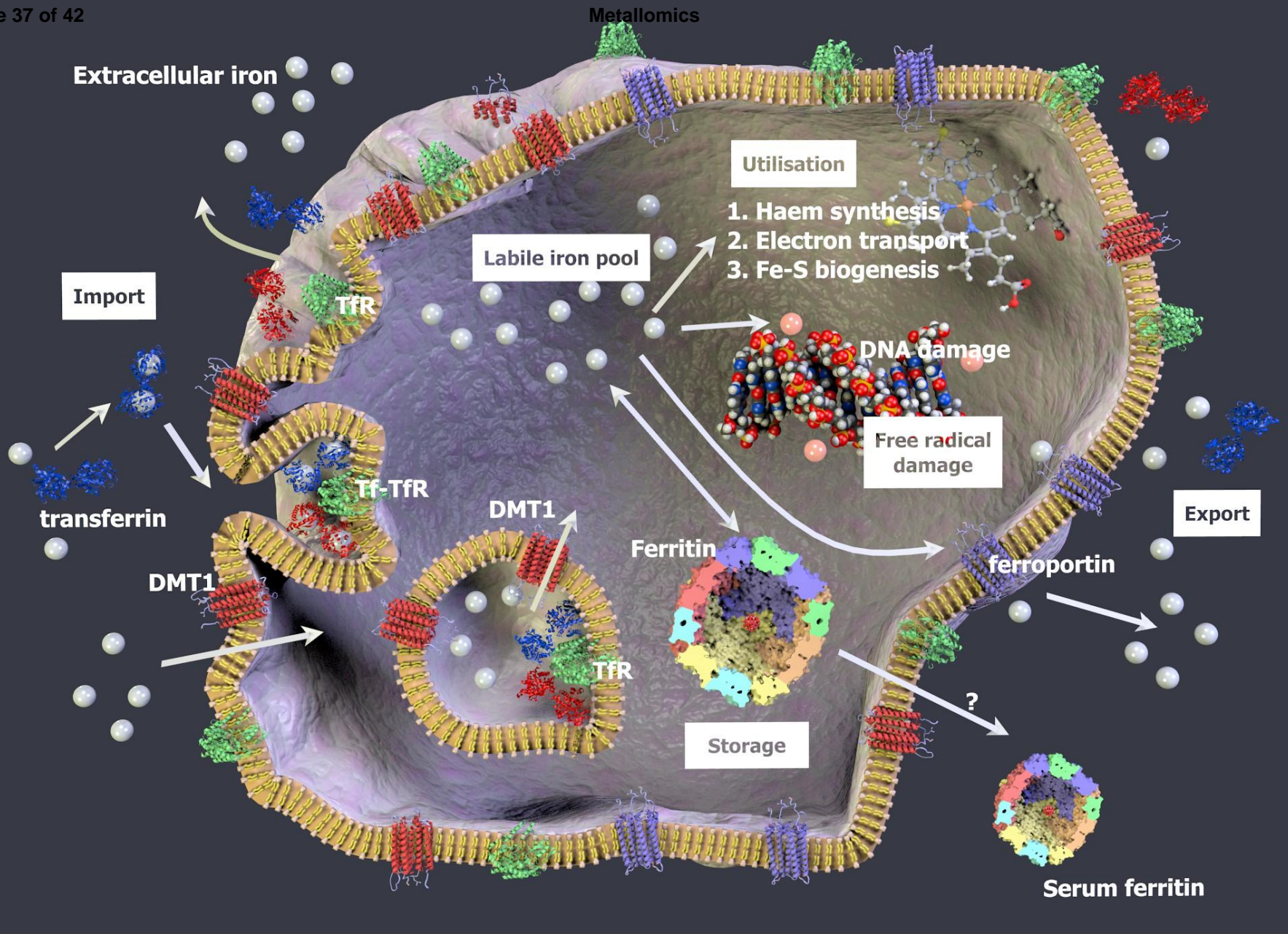
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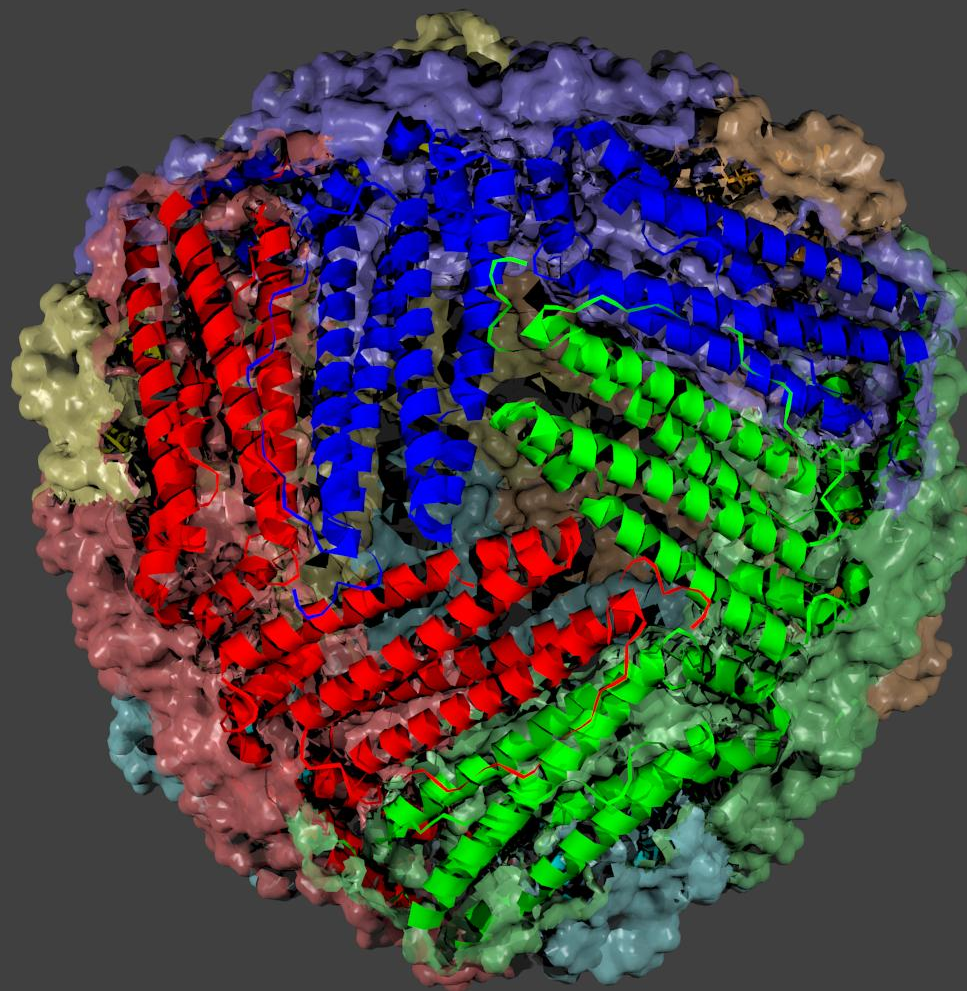
Kell & Pretorius, Fig 2

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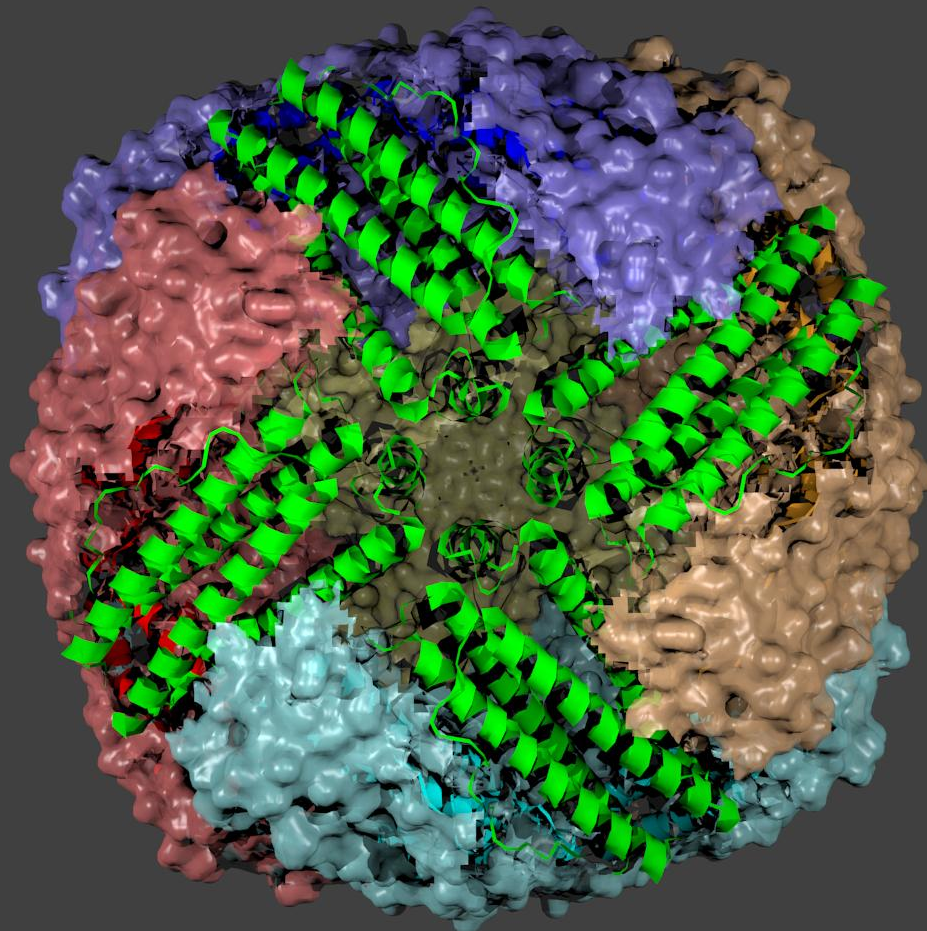
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Kell & Pretorius, Fig 3



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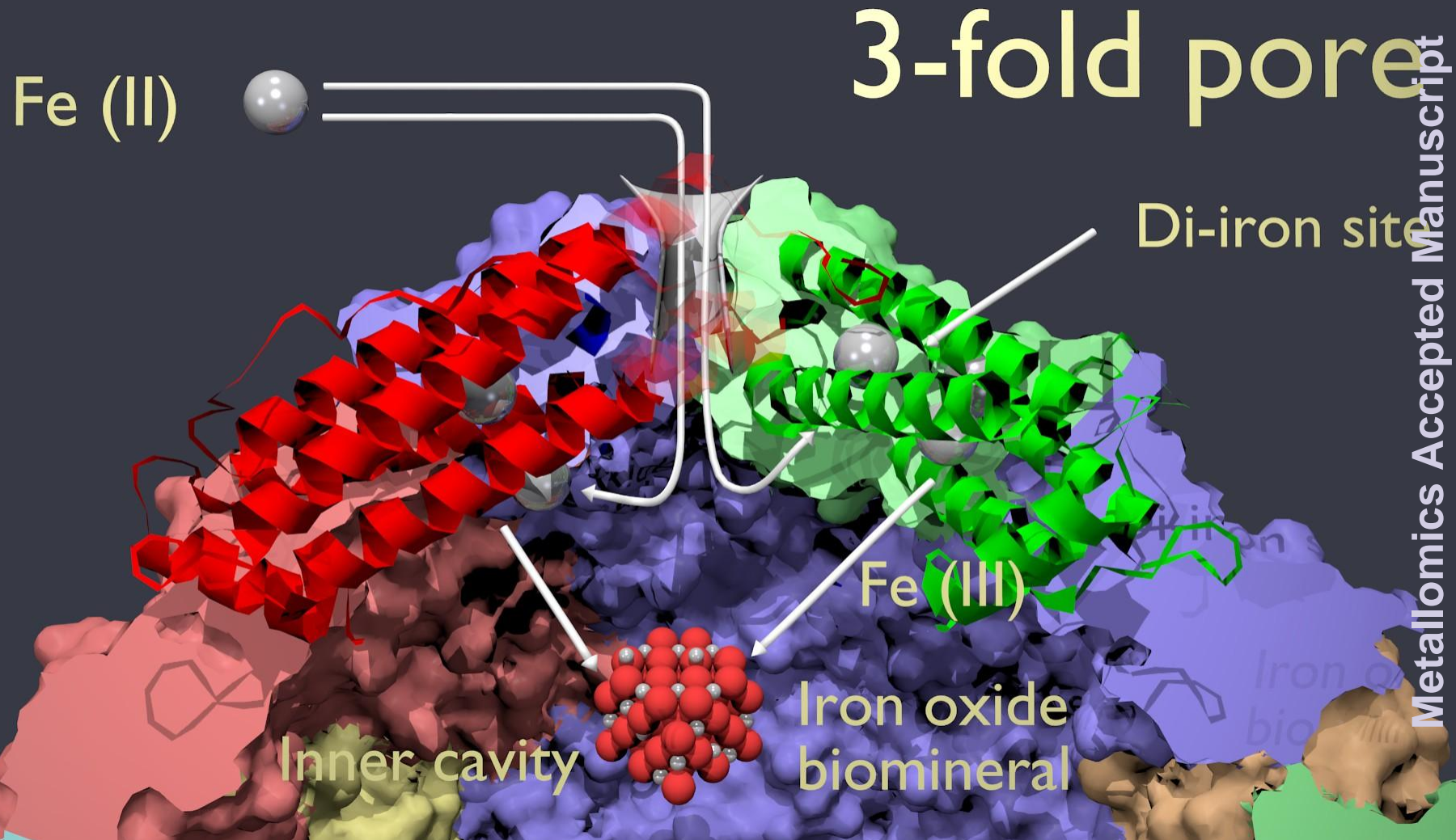
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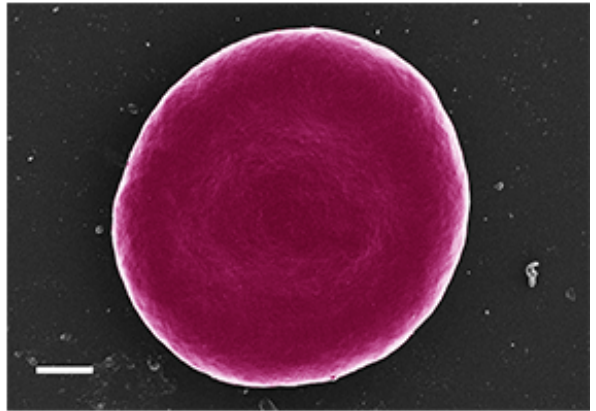
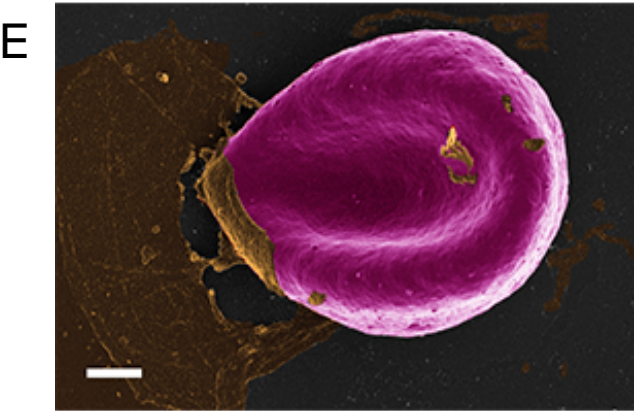
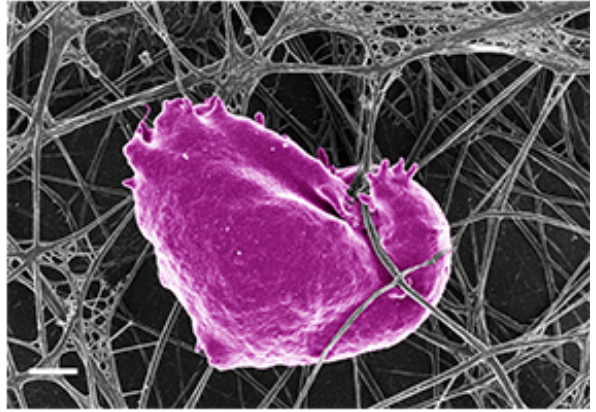
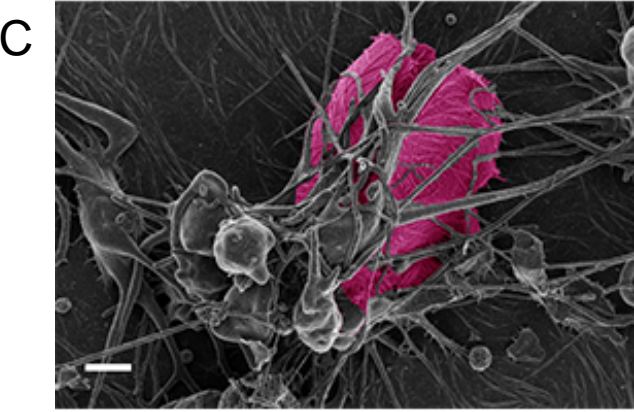
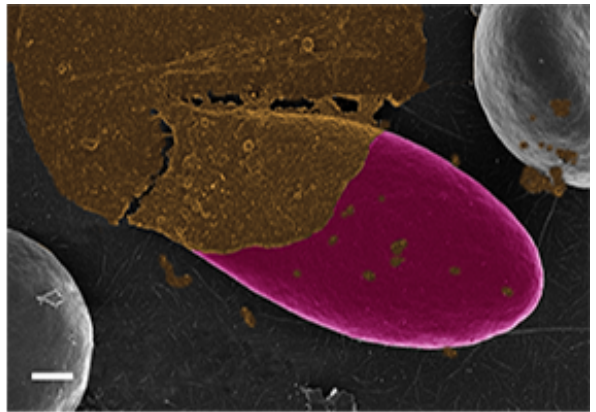
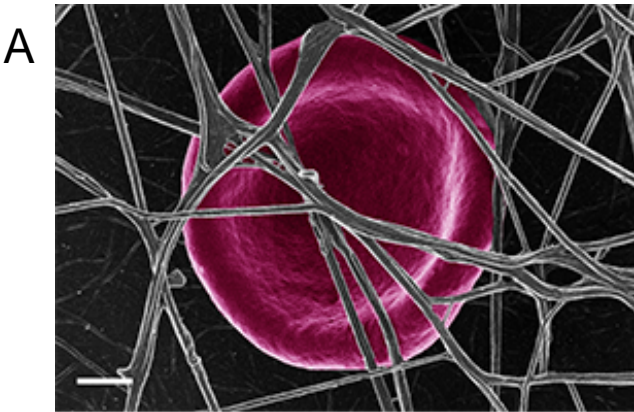
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# Iron uptake by ferritin

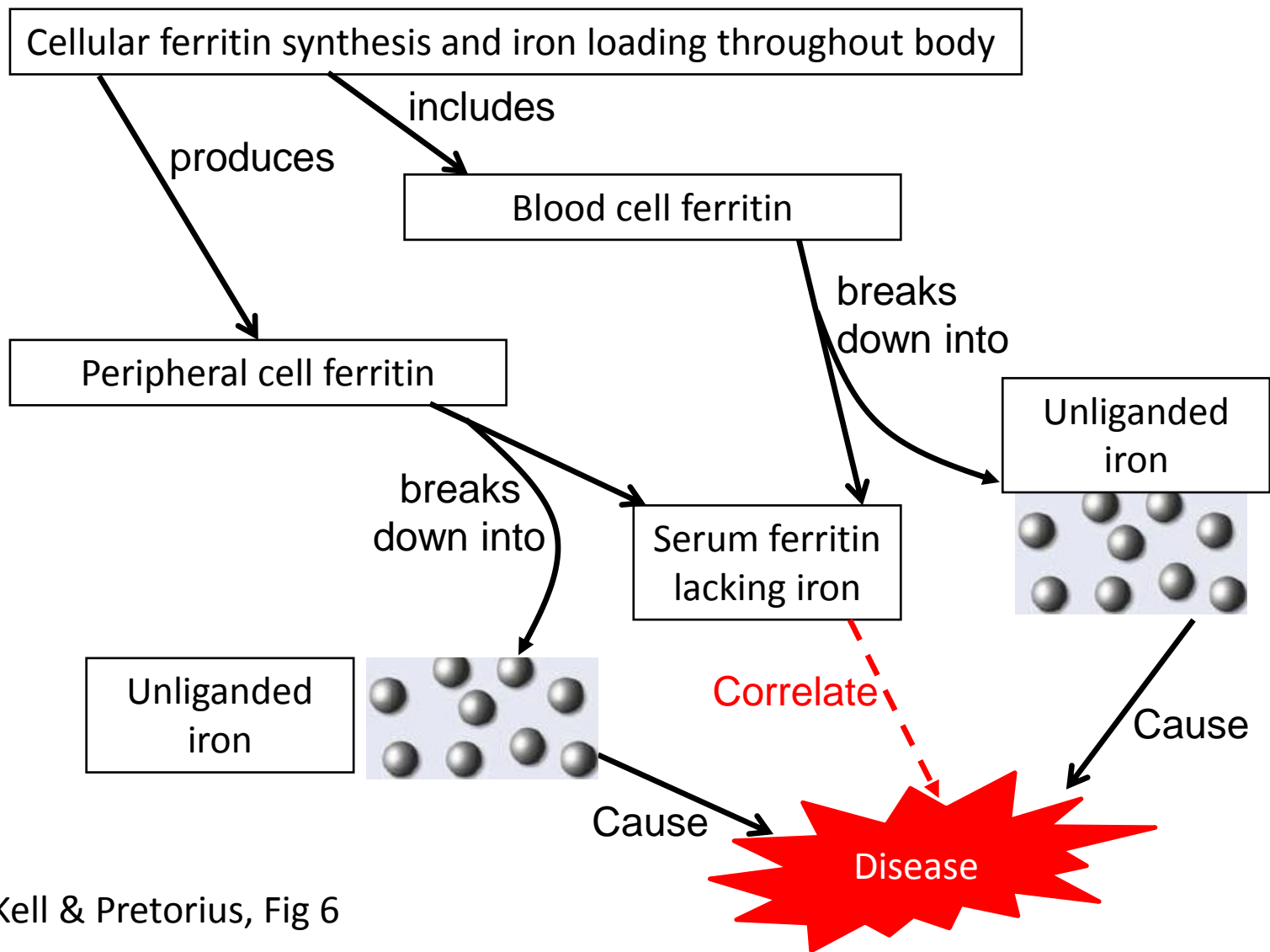


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# A high-level systems approach to serum ferritin



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