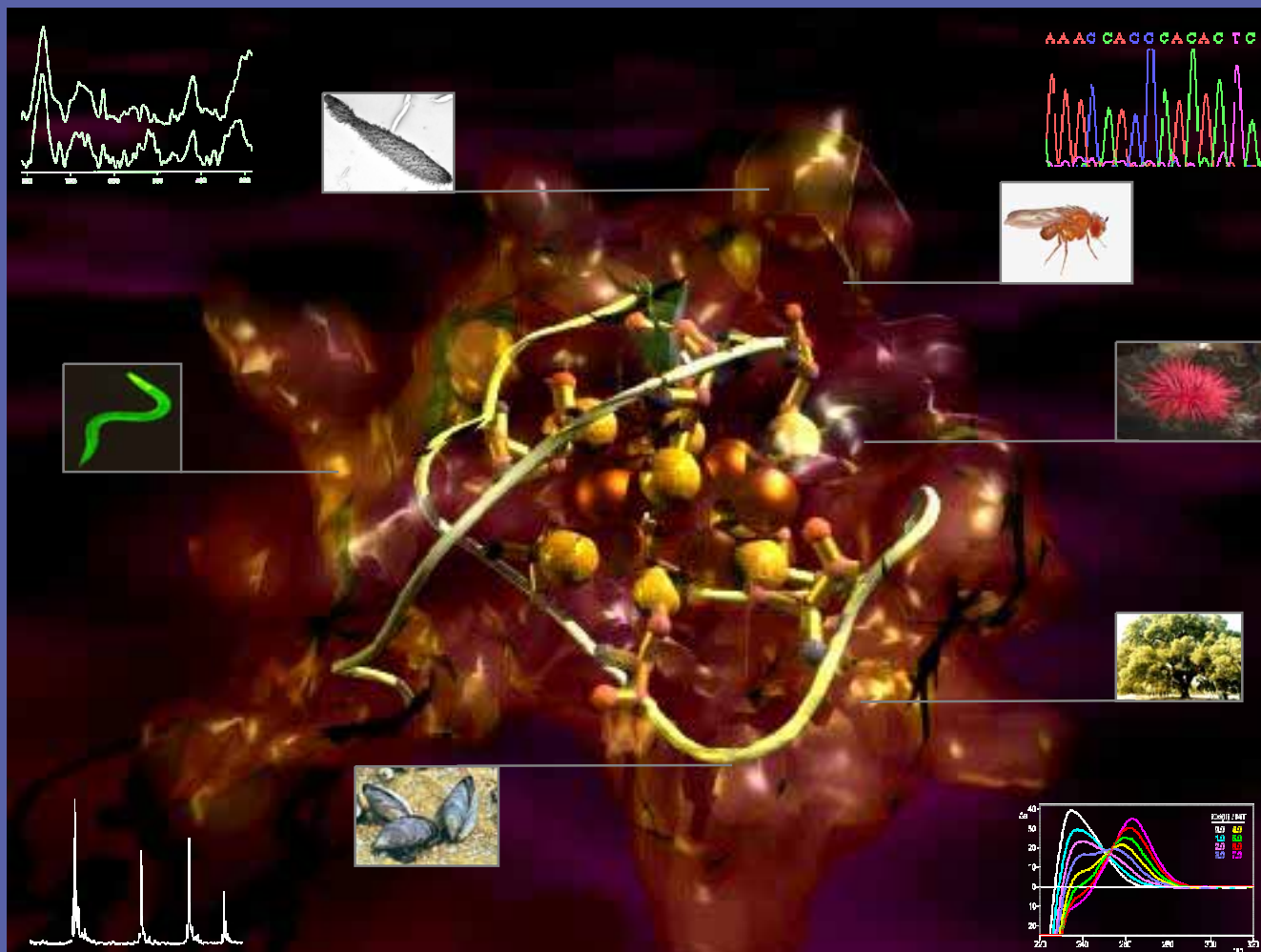


Estudi de la relació estructura/funció en Metal·lotioneïnes d'Invertebrats, Protozous i Plantes



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TESI DOCTORAL

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A

- Afonso, C., Hathout, Y. & Fenselau, C. (2004). Evidence for zinc ion sharing in metallothionein dimers provided by collision-induced dissociation. *Int-J.Mass.Spectr.* 231, 207-11.
- Amiard, J. C., Amiard-Triquet, C., Barka, S., Pellerin, J. & Rainbow, P. S. (2006). Metallothioneins in aquatic invertebrates: their role in metal detoxification and their use as biomarkers. *Aquat Toxicol* 76(2), 160-202.
- Andersen, R. A., Daae, H. L., Mikalsen, A. & Alexander, J. (1989). Occurrence of various forms of metallothionein in the rat after a short-term cadmium injection regimen. *Comp Biochem Physiol C* 93(2), 367-75.
- Andrews, G. K. (2001). Cellular zinc sensors: MTF-1 regulation of gene expression. *Biometals* 14(3-4), 223-37.
- Angerer, L. M., Kawczynski, G., Wilkinson, D. G., Nemer, M. & Angerer, R. C. (1986). Spatial patterns of metallothionein mRNA expression in the sea urchin embryo. *Dev Biol* 116(2), 543-7.
- Auld, D. S. (2001). Zinc coordination sphere in biochemical zinc sites. *Biometals* 14(3-4), 271-313.

B

- Barsyte, D., Lovejoy, D. A. & Lithgow, G. J. (2001). Longevity and heavy metal resistance in *daf-2* and *age-1* long-lived mutants of *Caenorhabditis elegans*. *Faseb J* 15(3), 627-34.
- Barsyte, D., White, K. N. & Lovejoy, D. A. (1999). Cloning and characterization of metallothionein cDNAs in the mussel *Mytilus edulis* L. digestive gland. *Comp Biochem Physiol C Pharmacol Toxicol Endocrinol* 122(2), 287-96.
- Bebianno, M. J. & Langston, W. J. (1993). Turnover rate of metallothionein and cadmium in *Mytilus edulis*. *Biometals* 6(4), 239-44.
- Belevich, I., Verkhovskiy, M. I. & Wikstrom, M. (2006). Proton-coupled electron transfer drives the proton pump of cytochrome c oxidase. *Nature* 440(7085), 829-32.
- Belle, C., Rammal, W. & Pierre, J. L. (2005). Sulfur ligation in copper enzymes and models. *J Inorg Biochem* 99(10), 1929-36.
- Berger, B., Dallinger, R., Gehrig, P. & Hunziker, P. E. (1997). Primary structure of a copper-binding metallothionein from mantle tissue of the terrestrial gastropod *Helix pomatia* L. *Biochem J* 328 (Pt 1), 219-24.
- Bertinato, J. & L'Abbe, M. R. (2004). Maintaining copper homeostasis: regulation of copper-trafficking proteins in response to copper deficiency or overload. *J Nutr Biochem* 15(6), 316-22.
- Bertini, I., Donaire, A., Feinberg, B. A., Luchinat, C., Piccioli, M. & Yuan, H. (1995). Solution structure of the oxidized [2[4Fe-4S] ferredoxin from *Clostridium pasteurianum*. *Eur J Biochem* 232(1), 192-205.
- Bertini, I., Hartmann, H. J., Klein, T., Liu, G., Luchinat, C. & Weser, U. (2000). High resolution solution structure of the protein part of Cu₇ metallothionein. *Eur J Biochem* 267(4), 1008-18.
- Bilecen, K., Ozturk, U. H., Duru, A. D., Sutlu, T., Petoukhov, M. V., Svergun, D. I., Koch, M. H., Sezerman, U. O., Cakmak, I. & Sayers, Z. (2005). *Triticum durum* metallothionein. Isolation of the gene and structural characterization of the protein using solution scattering and molecular modeling. *J Biol Chem* 280(14), 13701-11.
- Binz, P. A., Kägi, J. (2001). <http://www.biochem.unizh.ch/mtpage/MT.html>.
- Blindauer, C. A., Harrison, M. D., Parkinson, J. A., Robinson, A. K., Cavet, J. S., Robinson, N. J. & Sadler, P. J. (2001). A metallothionein containing a zinc finger within a four-metal cluster protects a bacterium from zinc toxicity. *Proc Natl Acad Sci U S A* 98(17), 9593-8.
- Bofill, R., Capdevila, M., Cols, N., Atrian, S. & Gonzalez-Duarte, P. (2001). Zinc(II) is required for the *in vivo* and *in vitro* folding of mouse copper metallothionein in two domains. *J Biol Inorg Chem* 6(4), 405-17.
- Bofill, R., Palacios, O., Capdevila, M., Cols, N., Gonzalez-Duarte, R., Atrian, S. & Gonzalez-Duarte, P. (1999). A new insight into the Ag⁺ and Cu⁺ binding sites in the metallothionein beta domain. *J Inorg Biochem* 73(1-2), 57-64.
- Boldrin, F., Santovito, G., Gaertig, J., Wloga, D., Cassidy-Hanley, D., Clark, T. G. & Piccinni, E. (2006). Metallothionein gene from *Tetrahymena thermophila* with a copper-inducible-repressible promoter. *Eukaryot Cell* 5(2), 422-5.
- Boldrin, F., Santovito, G., Irato, P. & Piccinni, E. (2002). Metal interaction and regulation of *Tetrahymena pigmentosa* metallothionein genes. *Protist* 153(3), 283-91.

- Boldrin, F., Santovito, G., Negrisolo, E. & Piccinni, E. (2003). Cloning and sequencing of four new metallothionein genes from *Tetrahymena thermophila* and *T. pigmentosa*: evolutionary relationships in *Tetrahymena* MT family. *Protist* 154(3-4), 431-42.
- Bongers, J., Walton, C. D., Richardson, D. E. & Bell, J. U. (1988). Micromolar protein concentrations and metalloprotein stoichiometries obtained by inductively coupled plasma atomic emission spectrometric determination of sulfur. *Anal Chem* 60(24), 2683-6.
- Bonneton, F., Theodore, L., Silar, P., Maroni, G. & Wegnez, M. (1996). Response of *Drosophila* metallothionein promoters to metallic, heat shock and oxidative stresses. *FEBS Lett* 380(1-2), 33-8.
- Brkljacic, J. M., Samardzic, J. T., Timotijevic, G. S. & Maksimovic, V. R. (2004). Expression analysis of buckwheat (*Fagopyrum esculentum* Moench) metallothionein-like gene (MT3) under different stress and physiological conditions. *J Plant Physiol* 161(6), 741-6.
- Brouwer, M., Syring, R. & Hoexum Brouwer, T. (2002). Role of a copper-specific metallothionein of the blue crab, *Callinectes sapidus*, in copper metabolism associated with degradation and synthesis of hemocyanin. *J Inorg Biochem* 88(2), 228-39.
- Buchanan-Wollaston, V. (1994). Isolation of cDNA clones for genes that are expressed during leaf senescence in *Brassica napus*. Identification of a gene encoding a senescence-specific metallothionein-like protein. *Plant Physiol* 105(3), 839-46.
- Butt, A., Mousley, C., Morris, K., Beynon, J., Can, C., Holub, E., Greenberg, J. T. & Buchanan-Wollaston, V. (1998). Differential expression of a senescence-enhanced metallothionein gene in *Arabidopsis* in response to isolates of *Peronospora parasitica* and *Pseudomonas syringae*. *Plant J* 16(2), 209-21.
- C**
- Cai, L., Satoh, M., Tohyama, C. & Cherian, M. G. (1999). Metallothionein in radiation exposure: its induction and protective role. *Toxicology* 132(2-3), 85-98.
- Calderone, V., Dolderer, B., Hartmann, H. J., Echner, H., Luchinat, C., Del Bianco, C., Mangani, S. & Weser, U. (2005). The crystal structure of yeast copper thionein: the solution of a long-lasting enigma. *Proc Natl Acad Sci U S A* 102(1), 51-6.
- Capasso, C., Carginale, V., Crescenzi, O., Di Maro, D., Parisi, E., Spadaccini, R. & Temussi, P. A. (2003). Solution structure of MT_{nc}, a novel metallothionein from the Antarctic fish *Notothenia coriiceps*. *Structure* 11(4), 435-43.
- Capdevila, M., Cols, N., Romero-Isart, N., Gonzalez-Duarte, R., Atrian, S. & Gonzalez-Duarte, P. (1997). Recombinant synthesis of mouse Zn₃-beta and Zn₄-alpha metallothionein 1 domains and characterization of their cadmium(II) binding capacity. *Cell Mol Life Sci* 53(8), 681-8.
- Cavaletto, M., Ghezzi, A., Burlando, B., Evangelisti, V., Ceratto, N. & Viarengo, A. (2002). Effect of hydrogen peroxide on antioxidant enzymes and metallothionein level in the digestive gland of *Mytilus galloprovincialis*. *Comp Biochem Physiol C Toxicol Pharmacol* 131(4), 447-55.
- Ceratto, N., Dondero, F., van de Loo, J. W., Burlando, B. & Viarengo, A. (2002). Cloning and sequencing of a novel metallothionein gene in *Mytilus galloprovincialis* Lam. *Comp Biochem Physiol C Toxicol Pharmacol* 131(3), 217-22.
- Chabicoovsky, M., Niederstatter, H., Thaler, R., Hodl, E., Parson, W., Rossmannith, W. & Dallinger, R. (2003). Localization and quantification of Cd- and Cu-specific metallothionein isoform mRNA in cells and organs of the terrestrial gastropod *Helix pomatia*. *Toxicol Appl Pharmacol* 190(1), 25-36.
- Cherian, M. G. & Kang, Y. J. (2006). Metallothionein and liver cell regeneration. *Exp Biol Med (Maywood)* 231(2), 138-44.
- Cho, S. H., Hoang, Q. T., Kim, Y. Y., Shin, H. Y., Ok, S. H., Bae, J. M. & Shin, J. S. (2006). Proteome analysis of gametophores identified a metallothionein involved in various abiotic stress responses in *Physcomitrella patens*. *Plant Cell Rep* 25(5), 475-88.
- Christianson, D. W. (1991). Structural biology of zinc. *Adv Protein Chem* 42, 281-355.
- Ciocan, C. M. & Rotchell, J. M. (2004). Cadmium induction of metallothionein isoforms in juvenile and adult mussel (*Mytilus edulis*). *Environ Sci Technol* 38(4), 1073-8.
- Clemens, S. (2006). Evolution and function of phytochelatin synthases. *J Plant Physiol* 163(3), 319-32.

- Clendennen, S. K. & May, G. D. (1997). Differential gene expression in ripening banana fruit. *Plant Physiol* 115(2), 463-9.
- Cobbett, C. & Goldsbrough, P. (2002). Phytochelatins and metallothioneins: roles in heavy metal detoxification and homeostasis. *Annu Rev Plant Biol* 53, 159-82.
- Cobine, P. A., McKay, R. T., Zangger, K., Dameron, C. T. & Armitage, I. M. (2004). Solution structure of Cu₆ metallothionein from the fungus *Neurospora crassa*. *Eur J Biochem* 271(21), 4213-21.
- Cols, N., Romero-Isart, N., Bofill, R., Capdevila, M., Gonzalez-Duarte, P., Gonzalez-Duarte, R. & Atrian, S. (1999). *In vivo* copper- and cadmium-binding ability of mammalian metallothionein beta domain. *Protein Eng* 12(3), 265-9.
- Cols, N., Romero-Isart, N., Capdevila, M., Oliva, B., Gonzalez-Duarte, P., Gonzalez-Duarte, R. & Atrian, S. (1997). Binding of excess cadmium(II) to Cd₇-metallothionein from recombinant mouse Zn₇-metallothionein 1. UV-vis absorption and circular dichroism studies and theoretical location approach by surface accessibility analysis. *J Inorg Biochem* 68(3), 157-66.
- Cook, W. J., Kar, S. R., Taylor, K. B. & Hall, L. M. (1998). Crystal structure of the cyanobacterial metallothionein repressor *SmtB*: a model for metalloregulatory proteins. *J Mol Biol* 275(2), 337-46.
- Coupe, S. A., Taylor, J. E. & Roberts, J. A. (1995). Characterisation of an mRNA encoding a metallothionein-like protein that accumulates during ethylene-promoted abscission of *Sambucus nigra* L. leaflets. *Planta* 197(3), 442-7.
- Coyle, P., Philcox, J. C., Carey, L. C. & Rofe, A. M. (2002). Metallothionein: the multipurpose protein. *Cell Mol Life Sci* 59(4), 627-47.
- Cserjesi, P., Fang, H. & Brandhorst, B. P. (1997). Metallothionein gene expression in embryos of the sea urchin *Lytechinus pictus*. *Mol Reprod Dev* 47(1), 39-46.
- Dallinger, R. (1996). Metallothionein research in terrestrial invertebrates: synopsis and perspectives. *Comp Biochem Physiol C Pharmacol Toxicol Endocrinol* 113(2), 125-33.
- Dallinger, R., Berger, B., Hunziker, P. & Kagi, J. H. (1997). Metallothionein in snail Cd and Cu metabolism. *Nature* 388(6639), 237-8.
- Dallinger, R., Berger, B., Hunziker, P. E., Birchler, N., Hauer, C. R. & Kagi, J. H. (1993). Purification and primary structure of snail metallothionein. Similarity of the N-terminal sequence with histones H4 and H2A. *Eur J Biochem* 216(3), 739-46.
- Dallinger, R., Chabicovsky, M., Lagg, B., Schipflinger, R., Weirich, H. G. & Berger, B. (2004). Isoform-specific quantification of metallothionein in the terrestrial gastropod *Helix pomatia*. II. A differential biomarker approach under laboratory and field conditions. *Environ Toxicol Chem* 23(4), 902-10.
- Dallinger, R., Wang, Y., Berger, B., Mackay, E. A. & Kagi, J. H. (2001). Spectroscopic characterization of metallothionein from the terrestrial snail, *Helix pomatia*. *Eur J Biochem* 268(15), 4126-33.
- Dalton, T., Fu, K., Enders, G. C., Palmiter, R. D. & Andrews, G. K. (1996). Analysis of the effects of overexpression of metallothionein-I in transgenic mice on the reproductive toxicology of cadmium. *Environ Health Perspect* 104(1), 68-76.
- Davies, C. & Robinson, S. P. (2000). Differential screening indicates a dramatic change in mRNA profiles during grape berry ripening. Cloning and characterization of cDNAs encoding putative cell wall and stress response proteins. *Plant Physiol* 122(3), 803-12.
- de Miranda, J. R., Thomas, M. A., Thurman, D. A. & Tomsett, A. B. (1990). Metallothionein genes from the flowering plant *Mimulus guttatus*. *FEBS Lett* 260(2), 277-80.
- Debec, A., Mokdad, R. & Wegnez, M. (1985). Metallothioneins and resistance to cadmium poisoning in *Drosophila* cells. *Biochem Biophys Res Commun* 127(1), 143-52.
- Degtyarenko, K. (2000). Bioinorganic motifs: towards functional classification of metalloproteins. *Bioinformatics* 16(10), 851-64.
- Dondero, F., Cavaletto, M., Ghezzi, A. R., La Terza, A., Banni, M. & Viarengo, A. (2004). Biochemical characterization and quantitative gene expression analysis of the multi-stress inducible metallothionein from *Tetrahymena thermophila*. *Protist* 155(2), 157-68.
- Dondero, F., Piacentini, L., Banni, M., Rebelo, M., Burlando, B. & Viarengo, A. (2005). Quantitative PCR analysis of two molluscan metallothionein genes unveils differential expression and regulation. *Gene* 345(2), 259-70.

D

- Dong, J., Song, M. O. & Freedman, J. H. (2005). Identification and characterization of a family of *Caenorhabditis elegans* genes that is homologous to the cadmium-responsive gene *cdr-1*. *Biochim Biophys Acta* 1727(1), 16-26.
- Durliat, M., Bonneton, F., Boissonneau, E., Andre, M. & Wegnez, M. (1995). Expression of metallothionein genes during the post-embryonic development of *Drosophila melanogaster*. *Biometals* 8(4), 339-51.
- ## E
- Egli, D., Domenech, J., Selvaraj, A., Balamurugan, K., Hua, H., Capdevila, M., Georgiev, O., Schaffer, W. & Atrian, S. (2006a). The four members of the *Drosophila* Metallothionein family exhibit distinct yet overlapping in heavy metal homeostasis and detoxification. *Genes to Cells* 11(6), 647-58.
- Egli, D., Selvaraj, A., Yepiskoposyan, H., Zhang, B., Hafen, E., Georgiev, O. & Schaffner, W. (2003). Knockout of 'metal-responsive transcription factor' MTF-1 in *Drosophila* by homologous recombination reveals its central role in heavy metal homeostasis. *Embo J* 22(1), 100-8.
- Egli, D., Yepiskoposyan, H., Selvaraj, A., Balamurugan, K., Rajaram, R., Simons, A., Multhaupt, G., Mettler, S., Vardanyan, A., Georgiev, O. & Schaffner, W. (2006b). A family knockout of all four *Drosophila* metallothioneins reveals a central role in copper homeostasis and detoxification. *Mol Cell Biol* 26(6), 2286-96.
- Elgren, T. E. & Wilcox, D. E. (1989). A unique low frequency Raman band associated with metal binding to metallothionein. *Biochem Biophys Res Commun* 163(2), 1093-9.
- ## F
- Fabris, D., Zaia, J., Hathout, Y., Fenselau, C. (1996). Retention of thiol protons in two classes of protein zinc coordination centers. *J. Am. Chem. Soc.* 118, 12242-3.
- Fang, X., Wu, J. & Wei, G. (1994). Radiolysis of metallothionein in deaerated and oxygen-saturated solutions. *Radiat Res* 138(2), 165-70.
- Ferrarello, C. N., Fernandez de la Campa, M. R., Carrasco, J. F. & Sanz-Medel, A. (2000). Speciation of metallothionein-like proteins of the mussel *Mytilus edulis* at basal levels by chromatographic separations coupled to quadrupole and double-focusing magnetic sector ICPMS. *Anal Chem* 72(24), 5874-80.
- Ferreri, C., Kratzsch, S., Landi, L. & Brede, O. (2005). Thiyl radicals in biosystems: effects on lipid structures and metabolisms. *Cell Mol Life Sci* 62(7-8), 834-47.
- Finney, L.A., O'Halloran, T.V. (2003). Transition Metal Speciation in the Cell: Insights from the Chemistry of Metal Ion Receptors. *Science* 300, 931-936.
- Foley, R. C., Liang, Z. M. & Singh, K. B. (1997). Analysis of type 1 metallothionein cDNAs in *Vicia faba*. *Plant Mol Biol* 33(4), 583-91.
- Fowler, B. A., Hildebrand, C. E., Kojima, Y. & Webb, M. (1987). Nomenclature of metallothionein. *Experientia Suppl* 52, 19-22.
- Freedman, J. H., Slice, L. W., Dixon, D., Fire, A. & Rubin, C. S. (1993). The novel metallothionein genes of *Caenorhabditis elegans*. Structural organization and inducible, cell-specific expression. *J Biol Chem* 268(4), 2554-64.
- Fu, C. & Miao, W. (2006). Cloning and Characterization of a New Multi-Stress Inducible Metallothionein Gene in *Tetrahymena pyriformis*. *Protist* 157(2), 193-203.
- Furey, W. F., Robbins, A. H., Clancy, L. L., Winge, D. R., Wang, B. C. & Stout, C. D. (1987). Crystal structure of Cd,Zn metallothionein. *Experientia Suppl* 52, 139-48.
- ## G
- Gan, T., Munoz, A., Shaw, C. F., 3rd & Petering, D. H. (1995). Reaction of ¹¹¹Cd7-metallothionein with EDTA. A reappraisal. *J Biol Chem* 270(10), 5339-45.
- Garcia-Hernandez, M., Murphy, A. & Taiz, L. (1998). Metallothioneins 1 and 2 have distinct but overlapping expression patterns in *Arabidopsis*. *Plant Physiol* 118(2), 387-97.
- Garza, A., Vega, R. & Soto, E. (2006). Cellular mechanisms of lead neurotoxicity. *Med Sci Monit* 12(3), RA57-65.
- Geffard, A., Amiard-Triquet, C. & Amiard, J. C. (2005). Do seasonal changes affect metallothionein induction by metals in mussels, *Mytilus edulis*? *Ecotoxicol Environ Saf* 61(2), 209-20.
- George, S. G. (1983). Heavy metal detoxication in the mussel *Mytilus edulis*-composition of Cd-containing kidney granules (tertiary lysosomes). *Comp Biochem Physiol C* 76(1), 53-7.
- Geret, F. & Cosson, R. P. (2002). Induction of specific isoforms of metallothionein in

- mussel tissues after exposure to cadmium or mercury. *Arch Environ Contam Toxicol* 42(1), 36-42.
- Ghoshal, K., Wang, Y., Sheridan, J. F. & Jacob, S. T. (1998). Metallothionein induction in response to restraint stress. Transcriptional control, adaptation to stress, and role of glucocorticoid. *J Biol Chem* 273(43), 27904-10.
- Giedroc, D. P., Chen, X. & Apuy, J. L. (2001). Metal response element (MRE)-binding transcription factor-1 (MTF-1): structure, function, and regulation. *Antioxid Redox Signal* 3(4), 577-96.
- Giles, G. I., Tasker, K. M. & Jacob, C. (2001). Hypothesis: the role of reactive sulfur species in oxidative stress. *Free Radic Biol Med* 31(10), 1279-83.
- Giritch, A., Ganal, M., Stephan, U. W. & Baumlein, H. (1998). Structure, expression and chromosomal localisation of the metallothionein-like gene family of tomato. *Plant Mol Biol* 37(4), 701-14.
- Gruber, C., Sturzenbaum, S., Gehrig, P., Sack, R., Hunziker, P., Berger, B. & Dallinger, R. (2000). Isolation and characterization of a self-sufficient one-domain protein. (Cd)-metallothionein from *Eisenia foetida*. *Eur J Biochem* 267(2), 573-82.
- Gupta, R. K., Dobritsa, S. V., Stiles, C. A., Essington, M. E., Liu, Z., Chen, C. H., Serpersu, E. H. & Mullin, B. C. (2002). Metallothioneins: a new class of plant metal-binding proteins. *J Protein Chem* 21(8), 529-36.
- ## H
- Hall, J. L. (2002). Cellular mechanisms for heavy metal detoxification and tolerance. *J Exp Bot* 53(366), 1-11.
- Hamer, D. H., Thiele, D. J. & Lemontt, J. E. (1985). Function and autoregulation of yeast copperthionein. *Science* 228(4700), 685-90.
- Haq, F., Mahoney, M. & Koropatnick, J. (2003). Signaling events for metallothionein induction. *Mutat Res* 533(1-2), 211-26.
- Hardivillier, Y., Leignel, V., Denis, F., Uguen, G., Cosson, R. & Laulier, M. (2004). Do organisms living around hydrothermal vent sites contain specific metallothioneins? The case of the genus *Bathymodiolus* (*Bivalvia*, *Mytilidae*). *Comp Biochem Physiol C Toxicol Pharmacol* 139(1-3), 111-8.
- Harlow, P., Watkins, E., Thornton, R. D. & Nemer, M. (1989). Structure of an ectodermally expressed sea urchin metallothionein gene and characterization of its metal-responsive region. *Mol Cell Biol* 9(12), 5445-55.
- Hathout, Y., Reynolds, K. J., Szilagy, Z. & Fenselau, C. (2002). Metallothionein dimers studied by nano-spray mass spectrometry. *J Inorg Biochem* 88(2), 119-22.
- Hawkes, S. J. (1997). What is a "Heavy Metal"? *Journal of Chemical Education* 74(11), 1374.
- Hayashi, Y., Nakagawa, C. W. & Murasugi, A. (1986). Unique properties of Cd-binding peptides induced in fission yeast, *Schizosaccharomyces pombe*. *Environ Health Perspect* 65, 13-9.
- Hensbergen, P. J., Donker, M. H., Van Velzen, M. J., Roelofs, D., Van Der Schors, R. C., Hunziker, E. & Van Straalen, N. M. (1999). Primary structure of a cadmium-induced metallothionein from the insect *Orchesella cincta* (*Collembola*). *Eur J Biochem* 259(1-2), 197-203.
- Howden, R., Goldsbrough, P. B., Andersen, C. R. & Cobbett, C. S. (1995). Cadmium-sensitive, cad1 mutants of *Arabidopsis thaliana* are phytochelatin deficient. *Plant Physiol* 107(4), 1059-66.
- ## I
- Imagawa, M., Onozawa, T., Okumura, K., Osada, S., Nishihara, T. & Kondo, M. (1990). Characterization of metallothionein cDNAs induced by cadmium in the nematode *Caenorhabditis elegans*. *Biochem J* 268(1), 237-40.
- Imbert, J., Culotta, V., Furst, P., Gedamu, L. & Hamer, D. (1990). Regulation of metallothionein gene transcription by metals. *Adv Inorg Biochem* 8, 139-64.
- ## J
- Jacob, C., Maret, W. & Vallee, B. L. (1998). Control of zinc transfer between thionein, metallothionein, and zinc proteins. *Proc Natl Acad Sci U S A* 95(7), 3489-94.
- Jenny, M. J., Ringwood, A. H., Schey, K., Warr, G. W. & Chapman, R. W. (2004). Diversity of metallothioneins in the American oyster, *Crassostrea virginica*, revealed by transcriptomic and proteomic approaches. *Eur J Biochem* 271(9), 1702-12.
- Jenny, M. J., Warr, G. W., Ringwood, A. H., Baltzegar, D. A. & Chapman, R. W. (2006). Regulation of metallothionein genes in the American oyster (*Crassostrea virginica*): Ontogeny and differential expression in

response to different stressors. *Gene* 379;156-65.

K

- Kägi, J. & Kojima, Y. (1987). Metallothionein II: Proceedings of the "Second international meeting on metallothionein and other low molecular weight metal-binding proteins". Birkhäuser, Basel.
- Kägi, J. & Vallee, B.L. (1960). Metallothionein: a cadmium- and zinc-containing protein from equine renal cortex. *J Biol Chem.* 235; 3460-5.
- Kar, S. R., Adams, A. C., Lebowitz, J., Taylor, K. B. & Hall, L. M. (1997). The cyanobacterial repressor *SmtB* is predominantly a dimer and binds two Zn²⁺ ions per subunit. *Biochemistry* 36(49), 15343-8.
- Kar, S. R., Lebowitz, J., Blume, S., Taylor, K. B. & Hall, L. M. (2001). *SmtB*-DNA and protein-protein interactions in the formation of the cyanobacterial metallothionein repression complex: Zn²⁺ does not dissociate the protein-DNA complex in vitro. *Biochemistry* 40(44), 13378-89.
- Kawashima, I., Kennedy, T. D., Chino, M. & Lane, B. G. (1992). Wheat *Ec* metallothionein genes. Like mammalian Zn²⁺ metallothionein genes, wheat Zn²⁺ metallothionein genes are conspicuously expressed during embryogenesis. *Eur J Biochem* 209(3), 971-6.
- Khoo, H. W. & Patel, K. H. (1999). Metallothionein cDNA, promoter, and genomic sequences of the tropical green mussel, *Perna viridis*. *J Exp Zool* 284(4), 445-53.
- Kille, P., Winge, D. R., Harwood, J. L. & Kay, J. (1991). A plant metallothionein produced in *E. coli*. *FEBS Lett* 295(1-3), 171-5.
- Klaassen, C. D. & Liu, J. (1998). Metallothionein transgenic and knock-out mouse models in the study of cadmium toxicity. *J Toxicol Sci* 23 Suppl 2, 97-102.
- Kondo, M., Imagawa, M., Maruyama, K., Okada, Y., Tsunasawa, S. & Nishihara, T. (1990). Biochemical and immunochemical characterization of *Caenorhabditis elegans* metallothioneins I and II induced by cadmium. *Biomed Environ Sci* 3(3), 315-25.
- Kugawa, F., Yamamoto, H., Osada, S., Aoki, M., Imagawa, M. & Nishihara, T. (1994). Metallothionein genes in the nematode *Caenorhabditis elegans* and metal inducibility in mammalian culture cells. *Biomed Environ Sci* 7(3), 222-31.

- Kulkarni, P. P., She, Y. M., Smith, S. D., Roberts, E. A. & Sarkar, B. (2006). Proteomics of metal transport and metal-associated diseases. *Chemistry* 12(9), 2410-22.
- Kumari, M. V., Hiramatsu, M. & Ebadi, M. (1998). Free radical scavenging actions of metallothionein isoforms I and II. *Free Radic Res* 29(2), 93-101.

L

- Lastowski-Perry, D., Otto, E. & Maroni, G. (1985a). Nucleotide sequence and expression of a *Drosophila* metallothionein. *J Biol Chem* 260(3), 1527-30.
- Lauverjat, S., Ballan-Dufrancais, C. & Wegnez, M. (1989). Detoxification of cadmium. Ultrastructural study and electron-probe microanalysis of the midgut in a cadmium-resistant strain of *Drosophila melanogaster*. *Biol Met* 2(2), 97-107.
- Lazo, J. S., Kondo, Y., Dellapiazza, D., Michalska, A. E., Choo, K. H. & Pitt, B. R. (1995). Enhanced sensitivity to oxidative stress in cultured embryonic cells from transgenic mice deficient in metallothionein I and II genes. *J Biol Chem* 270(10), 5506-10.
- Lecoeur, S., Videmann, B. & Berny, P. (2004). Evaluation of metallothionein as a biomarker of single and combined Cd/Cu exposure in *Dreissena polymorpha*. *Environ Res* 94(2), 184-91.
- Ledger, S. E. & Gardner, R. C. (1994). Cloning and characterization of five cDNAs for genes differentially expressed during fruit development of kiwifruit (*Actinidia deliciosa* var. *deliciosa*). *Plant Mol Biol* 25(5), 877-86.
- Lee, J., Shim, D., Song, W. Y., Hwang, I. & Lee, Y. (2004). *Arabidopsis* metallothioneins 2a and 3 enhance resistance to cadmium when expressed in *Vicia faba* guard cells. *Plant Mol Biol* 54(6), 805-15.
- Leignel, V., Hardivillier, Y. & Laulier, M. (2005). Small metallothionein *MT-10* genes in coastal and hydrothermal mussels. *Mar Biotechnol (NY)* 7(3), 236-44.
- Lemoine, S., Bigot, Y., Sellos, D., Cosson, R. P. & Laulier, M. (2000). Metallothionein Isoforms in *Mytilus edulis* (*Mollusca, Bivalvia*): Complementary DNA Characterization and Quantification of Expression in Different Organs after Exposure to Cadmium, Zinc, and Copper. *Mar Biotechnol (NY)* 2(2), 195-203.
- Lerch, K. (1980). Copper metallothionein, a copper-binding protein from *Neurospora crassa*. *Nature* 284(5754), 368-70.

- Liao, V. H. & Freedman, J. H. (1998). Cadmium-regulated genes from the nematode *Caenorhabditis elegans*. Identification and cloning of new cadmium-responsive genes by differential display. *J Biol Chem* 273(48), 31962-70.
- Lichtlen, P., Wang, Y., Belser, T., Georgiev, O., Certa, U., Sack, R. & Schaffner, W. (2001). Target gene search for the metal-responsive transcription factor MTF-1. *Nucleic Acids Res* 29(7), 1514-23.
- Lieb, B. (2003). A new metallothionein gene from the giant keyhole limpet *Megathura crenulata*. *Comp Biochem Physiol C Toxicol Pharmacol* 134(1), 131-7.
- Liu, J., Hara, C., Umeda, M., Zhao, Y., Okita, T. W. & Uchimiya, H. (1995a). Analysis of randomly isolated cDNAs from developing endosperm of rice (*Oryza sativa* L.): evaluation of expressed sequence tags, and expression levels of mRNAs. *Plant Mol Biol* 29(4), 685-9.
- Liu, J., Liu, Y., Hartley, D., Klaassen, C. D., Shehin-Johnson, S. E., Lucas, A. & Cohen, S. D. (1999). Metallothionein-I/II knockout mice are sensitive to acetaminophen-induced hepatotoxicity. *J Pharmacol Exp Ther* 289(1), 580-6.
- Liu, Y., Liu, J., Iszard, M. B., Andrews, G. K., Palmiter, R. D. & Klaassen, C. D. (1995b). Transgenic mice that overexpress metallothionein-I are protected from cadmium lethality and hepatotoxicity. *Toxicol Appl Pharmacol* 135(2), 222-8.
- ## M
- Mackay, E. A., Overnell, J., Dunbar, B., Davidson, I., Hunziker, P. E., Kagi, J. H. & Fothergill, J. E. (1993). Complete amino acid sequences of five dimeric and four monomeric forms of metallothionein from the edible mussel *Mytilus edulis*. *Eur J Biochem* 218(1), 183-94.
- Madden, E. F. (2003). The role of combined metal interactions in metal carcinogenesis: a review. *Rev Environ Health* 18(2), 91-109.
- Maret, W. (2004). Zinc and sulfur: a critical biological partnership. *Biochemistry* 43(12), 3301-9.
- Maret, W. (2005). Zinc coordination environments in proteins determine zinc functions. *J Trace Elem Med Biol* 19(1), 7-12.
- Maret, W., Heffron, G., Hill, H. A., Djuricic, D., Jiang, L. J. & Vallee, B. L. (2002). The ATP/metallothionein interaction: NMR and STM. *Biochemistry* 41(5), 1689-94.
- Maret, W., Larsen, K. S. & Vallee, B. L. (1997). Coordination dynamics of biological zinc "clusters" in metallothioneins and in the DNA-binding domain of the transcription factor Gal4. *Proc Natl Acad Sci U S A* 94(6), 2233-7.
- Margoshes, M. & Vallee, B. L. (1957). A cadmium protein from equine kidney cortex. *J Am Chem Soc* 79, 4813-4.
- Marino, F., Sturzenbaum, S. R., Kille, P. & Morgan, A. J. (1998). Cu-Cd interactions in earthworms maintained in laboratory microcosms: the examination of a putative copper paradox. *Comp Biochem Physiol C Pharmacol Toxicol Endocrinol* 120(2), 217-23.
- Maroni, G., Wise, J., Young, J. E. & Otto, E. (1987). Metallothionein gene duplications and metal tolerance in natural populations of *Drosophila melanogaster*. *Genetics* 117(4), 739-44.
- Masters, B. A., Kelly, E. J., Quaife, C. J., Brinster, R. L. & Palmiter, R. D. (1994). Targeted disruption of metallothionein I and II genes increases sensitivity to cadmium. *Proc Natl Acad Sci U S A* 91(2), 584-8.
- McNulty, M., Puljung, M., Jefford, G. & Dubreuil, R. R. (2001). Evidence that a copper-metallothionein complex is responsible for fluorescence in acid-secreting cells of the *Drosophila* stomach. *Cell Tissue Res* 304(3), 383-9.
- Meneghini, R. (1997). Iron homeostasis, oxidative stress, and DNA damage. *Free Radic Biol Med* 23(5), 783-92.
- Merrifield, M. E., Chaseley, J., Kille, P. & Stillman, M. J. (2006). Determination of the Cd/S cluster stoichiometry in *Fucus vesiculosus* metallothionein. *Chem Res Toxicol* 19(3), 365-75.
- Miseta, A. & Csutora, P. (2000). Relationship between the occurrence of cysteine in proteins and the complexity of organisms. *Mol Biol Evol* 17(8), 1232-9.
- Moilanen, L. H., Fukushige, T. & Freedman, J. H. (1999). Regulation of metallothionein gene transcription. Identification of upstream regulatory elements and transcription factors responsible for cell-specific expression of the metallothionein genes from *Caenorhabditis elegans*. *J Biol Chem* 274(42), 29655-65.
- Mokdad, R., Debec, A. & Wegnez, M. (1987). Metallothionein genes in *Drosophila melanogaster* constitute a dual system. *Proc Natl Acad Sci U S A* 84(9), 2658-62.
- Morris, C. A., Nicolaus, B., Sampson, V., Harwood, J. L. & Kille, P. (1999).

- Identification and characterization of a recombinant metallothionein protein from a marine alga, *Fucus vesiculosus*. *Biochem J* 338 (Pt 2), 553-60.
- Munoz, A., Forsterling, F. H., Shaw, C. F., 3rd & Petering, D. H. (2002). Structure of the (113)Cd(3)beta domains from *Homarus americanus* metallothionein-1: hydrogen bonding and solvent accessibility of sulfur atoms. *J Biol Inorg Chem* 7(7-8), 713-24.
- Murphy, A. & Taiz, L. (1995). Comparison of metallothionein gene expression and nonprotein thiols in ten *Arabidopsis* ecotypes. Correlation with copper tolerance. *Plant Physiol* 109(3), 945-54.
- Murphy, A., Zhou, J., Goldsbrough, P. B. & Taiz, L. (1997). Purification and immunological identification of metallothioneins 1 and 2 from *Arabidopsis thaliana*. *Plant Physiol* 113(4), 1293-301.
- ## N
- Nair, P. S. & Robinson, W. E. (1999). Purification and characterization of a histidine-rich glycoprotein that binds cadmium from the blood plasma of the bivalve *Mytilus edulis*. *Arch Biochem Biophys* 366(1), 8-14.
- Narula, S. S., Brouwer, M., Hua, Y. & Armitage, I. M. (1995). Three-dimensional solution structure of *Callinectes sapidus* metallothionein-1 determined by homonuclear and heteronuclear magnetic resonance spectroscopy. *Biochemistry* 34(2), 620-31.
- Nashef, A. S., Osuga, D. T. & Feeney, R. E. (1977). Determination of hydrogen sulfide with 5,5'-dithiobis-(2-nitrobenzoic acid), N-ethylmaleimide, and parachloromercuribenzoate. *Anal Biochem* 79(1-2), 394-405.
- Navabpour, S., Morris, K., Allen, R., Harrison, E., S, A. H.-M. & Buchanan-Wollaston, V. (2003). Expression of senescence-enhanced genes in response to oxidative stress. *J Exp Bot* 54(391), 2285-92.
- Nemer, M., Stuebing, E. W., Bai, G. & Parker, H. R. (1995). Spatial regulation of *SpMTA* metallothionein gene expression in sea urchin embryos by a regulatory cassette in intron 1. *Mech Dev* 50(2-3), 131-7.
- Nemer, M., Thornton, R. D., Stuebing, E. W. & Harlow, P. (1991). Structure, spatial, and temporal expression of two sea urchin metallothionein genes, *SpMTB1* and *SpMTA*. *J Biol Chem* 266(10), 6586-93.
- Nemer, M., Travaglini, E. C., Rondinelli, E. & D'Alonzo, J. (1984). Developmental regulation, induction, and embryonic tissue specificity of sea urchin metallothionein gene expression. *Dev Biol* 102(2), 471-82.
- Nemer, M., Wilkinson, D. G., Travaglini, E. C., Sternberg, E. J. & Butt, T. R. (1985). Sea urchin metallothionein sequence: key to an evolutionary diversity. *Proc Natl Acad Sci U S A* 82(15), 4992-4.
- Nettesheim, D. G., Engeseth, H. R. & Otvos, J. D. (1985). Products of metal exchange reactions of metallothionein. *Biochemistry* 24(24), 6744-51.
- ## O
- Ohtake, H., Suyemitsu, T. & Koga, M. (1983). Sea urchin (*Anthocidaris crassispina*) egg zinc-binding protein. Cellular localization, purification and characterization. *Biochem J* 211(1), 109-18.
- Olafson, R. W., McCubbin, W. D. & Kay, C. M. (1988). Primary- and secondary-structural analysis of a unique prokaryotic metallothionein from a *Synechococcus* sp. cyanobacterium. *Biochem J* 251(3), 691-9.
- Otvos, J. D., Liu, X., Li, H., Shen, G. & Basti, M. (1993). Dynamic Aspects of Metallothionein Structure. 55-74. Metallothionein III, Biological Roles and Medical Implications. Birkhäuser-Verlag, Basel, Switzerland.
- Otvos, J. D., Olafson, R. W. & Armitage, I. M. (1982). Structure of an invertebrate metallothionein from *Scylla serrata*. *J Biol Chem* 257(5), 2427-31.
- Oz, G., Zanger, K. & Armitage, I. M. (2001). Three-dimensional structure and dynamics of a brain specific growth inhibitory factor: metallothionein-3. *Biochemistry* 40(38), 11433-41.
- ## P
- Palmiter, R. D. (1998). The elusive function of metallothioneins. *Proc Natl Acad Sci U S A* 95(15), 8428-30.
- Palumaa, P., Mackay, E. A. & Vasak, M. (1992). Nonoxidative cadmium-dependent dimerization of Cd²⁺-metallothionein from rabbit liver. *Biochemistry* 31(7), 2181-6.
- Palumaa, P. & Vahter, M. (1996). Metal-induced dimerization of Cd²⁺-metallothionein. Role of anions. *Ann Clin Lab Sci* 26(3), 264-8.
- Palumaa, P., Zerbe, O. & Vasak, M. (1993). Formation and spectroscopic characterization of a novel monomeric cadmium- and phosphate-containing form

- of metallothionein. *Biochemistry* 32(11), 2874-9.
- Pande, J., Pande, C., Gilg, D., Vasak, M., Callender, R. & Kagi, J. H. (1986). Raman, infrared, and circular dichroism spectroscopic studies on metallothionein: a predominantly "turn"-containing protein. *Biochemistry* 25(19), 5526-32.
- Pande, J., Vasak, M. & Kagi, J. H. (1985). Interaction of lysine residues with the metal thiolate clusters in metallothionein. *Biochemistry* 24(23), 6717-22.
- Pena, M. M., Koch, K. A. & Thiele, D. J. (1998). Dynamic regulation of copper uptake and detoxification genes in *Saccharomyces cerevisiae*. *Mol Cell Biol* 18(5), 2514-23.
- Piccinni, E., Albergoni, V. (1996). Cadmium detoxification in Protists. *Comp. Biochem. Physiol. C* 113(2), 141-7.
- Piccinni, E., Bertaggia, D., Santovito, G., Miceli, C. & Kraev, A. (1999). Cadmium metallothionein gene of *Tetrahymena pyriformis*. *Gene* 234(1), 51-9.
- Piccinni, E., Irato, P., Coppellotti, O. & Guidolin, L. (1987). Biochemical and ultrastructural data on *Tetrahymena pyriformis* treated with copper and cadmium. *J Cell Sci* 88 (Pt 3), 283-93.
- Piccinni, E., Staudenmann, W., Albergoni, V., De Gabrieli, R. & James, P. (1994). Purification and primary structure of metallothioneins induced by cadmium in the protists *Tetrahymena pigmentosa* and *Tetrahymena pyriformis*. *Eur J Biochem* 226(3), 853-9.
- Pitt, B. R., Schwarz, M., Woo, E. S., Yee, E., Wasserloos, K., Tran, S., Weng, W., Mannix, R. J., Watkins, S. A., Tyurina, Y. Y., Tyurin, V. A., Kagan, V. E. & Lazo, J. S. (1997). Overexpression of metallothionein decreases sensitivity of pulmonary endothelial cells to oxidant injury. *Am J Physiol* 273(4 Pt 1), L856-65.
- ## Q
- Quaife, C. J., Findley, S. D., Erickson, J. C., Froelick, G. J., Kelly, E. J., Zambrowicz, B. P. & Palmiter, R. D. (1994). Induction of a new metallothionein isoform (MT-IV) occurs during differentiation of stratified squamous epithelia. *Biochemistry* 33(23), 7250-9.
- ## R
- Rhee, I. K., Lee, K. S. & Huang, P. C. (1990). Metallothioneins with interdomain hinges expanded by insertion mutagenesis. *Protein Eng* 3(3), 205-13.
- Riek, R., Precheur, B., Wang, Y., Mackay, E. A., Wider, G., Guntert, P., Liu, A., Kagi, J. H. & Wuthrich, K. (1999). NMR structure of the sea urchin (*Strongylocentrotus purpuratus*) metallothionein MTA. *J Mol Biol* 291(2), 417-28.
- Rigby, K. E., Chan, J., Mackie, J. & Stillman, M. J. (2006). Molecular dynamics study on the folding and metallation of the individual domains of metallothionein. *Proteins* 62(1), 159-72.
- Rigby, K. E. & Stillman, M. J. (2004). Structural studies of metal-free metallothionein. *Biochem Biophys Res Commun* 325(4), 1271-8.
- Robbins, A. H., McRee, D. E., Williamson, M., Collett, S. A., Xuong, N. H., Furey, W. F., Wang, B. C. & Stout, C. D. (1991). Refined crystal structure of Cd, Zn metallothionein at 2.0 Å resolution. *J Mol Biol* 221(4), 1269-93.
- Robinson, N. J., Barton, K., Naranjo, C. M., Sillerud, L. O., Trewhella, J., Watt, K. & Jackson, P. J. (1987). Characterization of metal binding peptides from cadmium resistant plant cells. *Experientia Suppl* 52, 323-7.
- Roesijadi, G., Kielland, S. & Klerks, P. (1989). Purification and properties of novel molluscan metallothioneins. *Arch Biochem Biophys* 273(2), 403-13.
- Romero-Isart, N., Cols, N., Termansen, M. K., Gelpi, J. L., Gonzalez-Duarte, R., Atrian, S., Capdevila, M. & Gonzalez-Duarte, P. (1999). Replacement of terminal cysteine with histidine in the metallothionein alpha and beta domains maintains its binding capacity. *Eur J Biochem* 259(1-2), 519-27.
- Roosens, N. H., Bernard, C., Leplae, R. & Verbruggen, N. (2004). Evidence for copper homeostasis function of metallothionein (MT3) in the hyperaccumulator *Thlaspi caerulescens*. *FEBS Lett* 577(1-2), 9-16.
- ## S
- Santovito, G., Irato, P., Palermo, S., Boldrin, F., Sack, R., Hunziker, P. & Piccinni, E. L. (2001). Identification, cloning and characterisation of a novel copper-metallothionein in *Tetrahymena pigmentosa*. Sequencing of cDNA and expression. *Protist* 152(3), 219-29.
- Sato, M. & Bremner, I. (1993). Oxygen free radicals and metallothionein. *Free Radic Biol Med* 14(3), 325-37.

- Scudiero, R., Capasso, C., Carginale, V., Riggio, M., Capasso, A., Ciaramella, M., Filosa, S. & Parisi, E. (1997). PCR amplification and cloning of metallothionein complementary DNAs in temperate and Antarctic sea urchin characterized by a large difference in egg metallothionein content. *Cell Mol Life Sci* 53(5), 472-7.
- Scudiero, R., Capasso, C., De Prisco, P. P., Capasso, A., Filosa, S. & Parisi, E. (1994). Metal-binding proteins in eggs of various sea urchin species. *Cell Biol Int* 18(1), 47-53.
- Scudiero, R., Temussi, P. A. & Parisi, E. (2005). Fish and mammalian metallothioneins: a comparative study. *Gene* 345(1), 21-6.
- Searle, P. F. (1990). Zinc dependent binding of a liver nuclear factor to metal response element MRE-a of the mouse metallothionein-I gene and variant sequences. *Nucleic Acids Res* 18(16), 4683-90.
- Serra, R., Isani, G., Tramontano, G. & Carpena, E. (1999). Seasonal dependence of cadmium accumulation and Cd-binding proteins in *Mytilus galloprovincialis* exposed to cadmium. *Comp Biochem Physiol C Pharmacol Toxicol Endocrinol* 123(2), 165-74.
- Shang, Y., Song, X., Bowen, J., Corstanje, R., Gao, Y., Gaertig, J. & Gorovsky, M. A. (2002). A robust inducible-repressible promoter greatly facilitates gene knockouts, conditional expression, and overexpression of homologous and heterologous genes in *Tetrahymena thermophila*. *Proc Natl Acad Sci U S A* 99(6), 3734-9.
- Sievers, C., Deters, D., Hartmann, H. J. & Weser, U. (1996). Stable thiyl radicals in dried yeast Cu(I)₆-thionein. *J Inorg Biochem* 62(3), 199-205.
- Silar, P., Theodore, L., Mokdad, R., Erraiss, N. E., Cadic, A. & Wegnez, M. (1990). Metallothionein Mto gene of *Drosophila melanogaster*: structure and regulation. *J Mol Biol* 215(2), 217-24.
- Silar, P. & Wegnez, M. (1990). Expression of the *Drosophila melanogaster* metallothionein genes in yeast. *FEBS Lett* 269(1), 273-6.
- Slice, L. W., Freedman, J. H. & Rubin, C. S. (1990). Purification, characterization, and cDNA cloning of a novel metallothionein-like, cadmium-binding protein from *Caenorhabditis elegans*. *J Biol Chem* 265(1), 256-63.
- Soazig, L. & Marc, L. (2003). Potential use of the levels of the mRNA of a specific metallothionein isoform (MT-20) in mussel (*Mytilus edulis*) as a biomarker of cadmium contamination. *Mar Pollut Bull* 46(11), 1450-5.
- Southon, A., Burke, R., Norgate, M., Batterham, P. & Camakaris, J. (2004). Copper homeostasis in *Drosophila melanogaster* S2 cells. *Biochem J* 383(Pt 2), 303-9.
- Sturzenbaum, S. R., Georgiev, O., Morgan, A. J. & Kille, P. (2004). Cadmium detoxification in earthworms: from genes to cells. *Environ Sci Technol* 38(23), 6283-9.
- Suzuki, K. T., Ohnuki, R. & Yaguchi, K. (1983). Post-mortem and in vitro dimerization of metallothionein in cadmium-accumulated rat liver and kidney. *Toxicol Lett* 16(1-2), 77-84.
- Swain, S. C., Keusekotten, K., Baumeister, R. & Sturzenbaum, S. R. (2004). *C. elegans* metallothioneins: new insights into the phenotypic effects of cadmium toxicosis. *J Mol Biol* 341(4), 951-59.
- Syring, R. A., Hoexum Brouwer, T. & Brouwer, M. (2000). Cloning and sequencing of cDNAs encoding for a novel copper-specific metallothionein and two cadmium-inducible metallothioneins from the blue crab *Callinectes sapidus*. *Comp Biochem Physiol C Toxicol Pharmacol* 125(3), 325-32.
- ## T
- Tang, W., Kido, T., Gross, W. A., Nogawa, K., Sabbioni, E. & Shaikh, Z. A. (1999). Measurement of cadmium-induced metallothionein in urine by ELISA and prevention of overestimation due to polymerization. *J Anal Toxicol* 23(3), 153-8.
- Tanguy, A., Boutet, I., Bonhomme, F., Boudry, P. & Moraga, D. (2002). Polymorphism of metallothionein genes in the Pacific oyster *Crassostrea gigas* as a biomarker of response to metal exposure. *Biomarkers* 7(6), 439-50.
- Tanguy, A. & Moraga, D. (2001). Cloning and characterization of a gene coding for a novel metallothionein in the Pacific oyster *Crassostrea gigas* (CgMT2): a case of adaptive response to metal-induced stress? *Gene* 273(1), 123-30.
- Templeton, D. M. & Cherian, M. G. (1985). Chemical modifications of metallothionein, II. Metabolic fate of cadmium bound to metallothionein polymers. *Toxicol Lett* 25(3), 279-86.
- Theocharis, S. E., Margeli, A. P., Klijanienko, J. T. & Kouraklis, G. P. (2004). Metallothionein expression in human neoplasia. *Histopathology* 45(2), 103-18.

- Thornalley, P. J. & Vasak, M. (1985). Possible role for metallothionein in protection against radiation-induced oxidative stress. Kinetics and mechanism of its reaction with superoxide and hydroxyl radicals. *Biochim Biophys Acta* 827(1), 36-44.
- Timmermans, M. J., Eilers, J., Roelofs, D. & van Straalen, N. M. (2005). Metallothionein mRNA expression and cadmium tolerance in metal-stressed and reference populations of the springtail *Orchesella cincta*. *Ecotoxicology* 14(7), 727-39.
- Tio, L., Villarreal, L., Atrian, S. & Capdevila, M. (2004). Functional differentiation in the mammalian metallothionein gene family: metal binding features of mouse MT4 and comparison with its paralog MT1. *J Biol Chem* 279(23), 24403-13.
- Tommey, A. M., Shi, J., Lindsay, W. P., Urwin, P. E. & Robinson, N. J. (1991). Expression of the pea gene PSMTA in *E. coli*. Metal-binding properties of the expressed protein. *FEBS Lett* 292(1-2), 48-52.
- Tucker, S. L., Thornton, C. R., Tasker, K., Jacob, C., Giles, G., Egan, M. & Talbot, N. J. (2004). A fungal metallothionein is required for pathogenicity of *Magnaporthe grisea*. *Plant Cell* 16(6), 1575-88.
- ## U
- Uchida, Y., Takio, K., Titani, K., Ihara, Y. & Tomonaga, M. (1991). The growth inhibitory factor that is deficient in the Alzheimer's disease brain is a 68 amino acid metallothionein-like protein. *Neuron* 7(2), 337-47.
- ## V
- Vallee, B. L. & Auld, D. S. (1990). Zinc coordination, function, and structure of zinc enzymes and other proteins. *Biochemistry* 29(24), 5647-59.
- Valls, M., Bofill, R., Gonzalez-Duarte, R., Gonzalez-Duarte, P., Capdevila, M. & Atrian, S. (2001). A new insight into metallothionein (MT) classification and evolution. The in vivo and in vitro metal binding features of *Homarus americanus* recombinant MT. *J Biol Chem* 276(35), 32835-43.
- Valls, M., Bofill, R., Romero-Isart, N., Gonzalez-Duarte, R., Abian, J., Carrascal, M., Gonzalez-Duarte, P., Capdevila, M. & Atrian, S. (2000). *Drosophila* MTN: a metazoan copper-thionein related to fungal forms. *FEBS Lett* 467(2-3), 189-94.
- Vasak, M. (1991). Metal removal and substitution in vertebrate and invertebrate metallothioneins. *Methods Enzymol* 205, 452-8.
- Vasak, M. (2005). Advances in metallothionein structure and functions. *J Trace Elem Med Biol* 19(1), 13-7.
- Vatamaniuk, O. K., Bucher, E. A., Sundaram, M. V. & Rea, P. A. (2005). *CeHMT-1*, a putative phytochelatin transporter, is required for cadmium tolerance in *Caenorhabditis elegans*. *J Biol Chem* 280(25), 23684-90.
- Vatamaniuk, O. K., Bucher, E. A., Ward, J. T. & Rea, P. A. (2001). A new pathway for heavy metal detoxification in animals. Phytochelatin synthase is required for cadmium tolerance in *Caenorhabditis elegans*. *J Biol Chem* 276(24), 20817-20.
- Vergani, L., Grattarola, M., Borghi, C., Dondero, F. & Viarengo, A. (2005). Fish and molluscan metallothioneins. *Febs J* 272(23), 6014-23.
- Viarengo, A., Burlando, B., Cavaletto, M., Marchi, B., Ponzano, E. & Blasco, J. (1999). Role of metallothionein against oxidative stress in the mussel *Mytilus galloprovincialis*. *Am J Physiol* 277(6 Pt 2), R1612-9.
- Viarengo, A., Burlando, B., Ceratto, N. & Panfoli, I. (2000). Antioxidant role of metallothioneins: a comparative overview. *Cell Mol Biol (Noisy-le-grand)* 46(2), 407-17.
- Villarreal, L., Tio, L., Atrian, S. & Capdevila, M. (2005). Influence of chloride ligands on the structure of Zn- and Cd-metallothionein species. *Arch Biochem Biophys* 435(2), 331-5.
- Villarreal, L., Tio, L., Capdevila, M. & Atrian, S. (2006). Comparative metal binding and genomic analysis of the avian (chicken) and mammalian metallothionein. *Febs J* 273(3), 523-35.
- ## W
- Wachtershauser, G. (1988). Before enzymes and templates: theory of surface metabolism. *Microbiol Rev* 52(4), 452-84.
- Wagner, G., Frey, M. H., Neuhaus, D., Worgotter, E., Braun, W., Vasak, M., Kagi, J. H. & Wuthrich, K. (1987). Spatial structure of rabbit liver metallothionein-2 in solution by NMR. *Experientia Suppl* 52, 149-57.
- Wang, H., Zhang, Q., Cai, B., Li, H., Sze, K. H., Huang, Z. X., Wu, H. M. & Sun, H. (2006). Solution structure and dynamics of human

- metallothionein-3 (MT-3). *FEBS Lett* 580(3), 795-800.
- Wang, Y., Mackay, E. A., Kurasaki, M. & Kagi, J. H. (1994). Purification and characterisation of recombinant sea urchin metallothionein expressed in *Escherichia coli*. *Eur J Biochem* 225(1), 449-57.
- Wang, Y., Mackay, E. A., Zerbe, O., Hess, D., Hunziker, P. E., Vasak, M. & Kagi, J. H. (1995). Characterization and sequential localization of the metal clusters in sea urchin metallothionein. *Biochemistry* 34(22), 7460-7.
- Wilhelmsen, T. W., Olsvik, P. A., Hansen, B. H. & Andersen, R. A. (2002). Evidence for oligomerization of metallothioneins in their functional state. *J Chromatogr A* 979(1-2), 249-54.
- Wilkinson, D. G. & Nemer, M. (1987). Metallothionein genes *MTa* and *MTb* expressed under distinct quantitative and tissue-specific regulation in sea urchin embryos. *Mol Cell Biol* 7(1), 48-58.
- Willuhn, J., Schmitt-Wrede, H. P., Greven, H. & Wunderlich, F. (1994). cDNA cloning of a cadmium-inducible mRNA encoding a novel cysteine-rich, non-metallothionein 25-kDa protein in an enchytraeid earthworm. *J Biol Chem* 269(40), 24688-91.
- Winge, D., Dameron, C. T. & Mehra, R. K. (1992). Metal:Sulfide Quantum Crystallites in Yeast. In Stillman, M.J., Shaw, C.F., 3rd & KT, S. (Eds.), *Metallothioneins* pp. 257-70. New York: VCH.
- Winge, D. R. & Miklossy, K. A. (1982). Differences in the polymorphic forms of metallothionein. *Arch Biochem Biophys* 214(1), 80-8.
- Winge, D. R., Nielson, K. B., Gray, W. R. & Hamer, D. H. (1985). Yeast metallothionein. Sequence and metal-binding properties. *J Biol Chem* 260(27), 14464-70.
- metallothioneins. *J Inorg Biochem* 88(2), 135-43.
- Zangger, K., Oz, G., Otvos, J. D. & Armitage, I. M. (1999). Three-dimensional solution structure of mouse [Cd⁷]-metallothionein-1 by homonuclear and heteronuclear NMR spectroscopy. *Protein Sci* 8(12), 2630-8.
- Zangger, K., Shen, G., Oz, G., Otvos, J. D. & Armitage, I. M. (2001). Oxidative dimerization in metallothionein is a result of intermolecular disulphide bonds between cysteines in the alpha-domain. *Biochem J* 359(Pt 2), 353-60.
- Zhang, B., Egli, D., Georgiev, O. & Schaffner, W. (2001). The *Drosophila* homolog of mammalian zinc finger factor MTF-1 activates transcription in response to heavy metals. *Mol Cell Biol* 21(14), 4505-14.
- Zhou, G. K., Xu, Y. F. & Liu, J. Y. (2005). Characterization of a rice class II metallothionein gene: tissue expression patterns and induction in response to abiotic factors. *J Plant Physiol* 162(6), 686-96.
- Zhou, J. & Goldsbrough, P. B. (1994). Functional homologs of fungal metallothionein genes from *Arabidopsis*. *Plant Cell* 6(6), 875-84.
- Zhu, C., Lü, T., Zhang, R., Zhao, N., Liu, J. (2000). Modeling of kiwifruit metallothionein *Kiwi503*. *Chinese Science Bulletin* 45(15), 1413-7.
- Zhu, Z., DeRose, E. F., Mullen, G. P., Petering, D. H. & Shaw, C. F., 3rd. (1994). Sequential proton resonance assignments and metal cluster topology of lobster metallothionein-1. *Biochemistry* 33(30), 8858-65.
- Zimeri, A. M., Dhankher, O. P., McCaig, B. & Meagher, R. B. (2005). The plant MT1 metallothioneins are stabilized by binding cadmiums and are required for cadmium tolerance and accumulation. *Plant Mol Biol* 58(6), 839-55.

Y

- You, C., Mackay, E. A., Gehrig, P. M., Hunziker, P. E. & Kagi, J. H. (1999). Purification and characterization of recombinant *Caenorhabditis elegans* metallothionein. *Arch Biochem Biophys* 372(1), 44-52.

Z

- Zangger, K. & Armitage, I. M. (2002). Dynamics of interdomain and intermolecular interactions in mammalian