

Tesi Doctoral

**EFFECTES DE FÀRMACS INTERCALANTS DEL
DNA EN L'EXPRESSIÓ GÈNICA A
*Saccharomyces cerevisiae***

Marta Rojas Amadó



Barcelona, Setembre 2007

DEPARTAMENT DE BIOQUÍMICA I BIOLOGIA MOLECULAR
Programa de Doctorat de Biomedicina
Bienni 2002-2004

**EFFECTES DE FÀRMACS INTERCALANTS DEL DNA EN L'EXPRESSIÓ
GÈNICA A *Saccharomyces cerevisiae***

Memòria presentada per **Marta Rojas Amadó**

Per optar al grau de Doctora per la Universitat de Barcelona

**Tesis Doctoral realizada en el Departament de Biología
Molecular i Cel·lular de l'Institut de Biología Molecular de Barcelona
(IBMB-CSIC)**

Directors

José Portugal Minguela

Benjamin Piña Capó

Tutor

Rafael Franco Fernández

Bibliografia

- Alberola, T. M., García-Martínez, J., Antúnez, O., Viladevall, L., Barceló, A., Ariño, J., and Pérez-Ortín, J. E. (2004). A new set of DNA macrochips for the yeast *Saccharomyces cerevisiae*: features and uses. *Int Microbiol* 7, 199-206.
- Albrecht, G., Mosch, H. U., Hoffmann, B., Reusser, U., and Braus, G. H. (1998). Monitoring the Gcn4 protein-mediated response in the yeast *Saccharomyces cerevisiae*. *J Biol Chem* 273, 12696-12702.
- Alwine, J. C., Kemp, D. J., and Stark, G. R. (1977). Method for detection of specific RNAs in agarose gels by transfer to diazobenzyloxymethyl-paper and hybridization with DNA probes. *Proc Natl Acad Sci U S A* 74, 5350-5354.
- Anderson, J. B., Sirjusingh, C., Parsons, A. B., Boone, C., Wickens, C., Cowen, L. E., and Kohn, L. M. (2003). Mode of selection and experimental evolution of antifungal drug resistance in *Saccharomyces cerevisiae*. *Genetics* 163, 1287-1298.
- Ansah, C., and Gooderham, N. J. (2002). The popular herbal antimalarial, extract of *Cryptolepis sanguinolenta*, is potently cytotoxic. *Toxicol Sci* 70, 245-251.
- Ansah, C., Khan, A., and Gooderham, N. J. (2005). In vitro genotoxicity of the West African anti-malarial herbal *Cryptolepis sanguinolenta* and its major alkaloid cryptolepine. *Toxicology* 208, 141-147.
- Arzel, E., Rocca, P., Grellier, P., Labaeid, M., Frappier, F., Gueritte, F., Gaspard, C., Marsais, F., Godard, A., and Queguiner, G. (2001). New synthesis of benzo-delta-carbolines, cryptolepines, and their salts: in vitro cytotoxic, antiplasmodial, and antitrypanosomal activities of delta-carbolines, benzo-delta-carbolines, and cryptolepines. *J Med Chem* 44, 949-960.
- Banzouzi, J. T., Prado, R., Menan, H., Valentin, A., Roumestan, C., Mallie, M., Pelissier, Y., and Blache, Y. (2004). Studies on medicinal plants of Ivory Coast: investigation of *Sida acuta* for in vitro antiplasmodial activities and identification of an active constituent. *Phytomedicine* 11, 338-341.
- Bedalov, A., Gatbonton, T., Irvine, W. P., Gottschling, D. E., and Simon, J. A. (2001). Identification of a small molecule inhibitor of Sir2p. *Proc Natl Acad Sci U S A* 98, 15113-15118.
- Bender, A., and Pringle, J. R. (1991). Use of a screen for synthetic lethal and multicopy suppressor mutants to identify two new genes involved in morphogenesis in *Saccharomyces cerevisiae*. *Mol Cell Biol* 11, 1295-1305.
- Benton, M. G., Somasundaram, S., Glasner, J. D., and Palecek, S. P. (2006). Analyzing the dose-dependence of the *Saccharomyces cerevisiae* global transcriptional response to methyl methanesulfonate and ionizing radiation. *BMC Genomics* 7, 305.
- Berman, H. M., and Young, P. R. (1981). The interaction of intercalating drugs with nucleic acids. *Annu Rev Biophys Bioeng* 10, 87-114.

- Binaschi, M., Bigioni, M., Cipollone, A., Rossi, C., Goso, C., Maggi, C. A., Capranico, G., and Animati, F. (2001). Anthracyclines: selected new developments. *Curr Med Chem Anticancer Agents 1*, 113-130.
- Birrell, G. W., Brown, J. A., Wu, H. I., Giaevers, G., Chu, A. M., Davis, R. W., and Brown, J. M. (2002). Transcriptional response of *Saccharomyces cerevisiae* to DNA-damaging agents does not identify the genes that protect against these agents. *Proc Natl Acad Sci U S A 99*, 8778-8783.
- Bitter, G. A., Chang, K. K., and Egan, K. M. (1991). A multi-component upstream activation sequence of the *Saccharomyces cerevisiae* glyceraldehyde-3-phosphate dehydrogenase gene promoter. *Mol Gen Genet 231*, 22-32.
- Blasco, M. A. (2007). The epigenetic regulation of mammalian telomeres. *Nat Rev Genet 8*, 299-309.
- Bonjean, K., De Pauw-Gillet, M. C., Defresne, M. P., Colson, P., Houssier, C., Dassonneville, L., Bailly, C., Greimers, R., Wright, C., Quentin-Leclercq, J., et al. (1998). The DNA intercalating alkaloid cryptolepine interferes with topoisomerase II and inhibits primarily DNA synthesis in B16 melanoma cells. *Biochemistry 37*, 5136-5146.
- Booser, D. J., and Hortobagyi, G. N. (1994). Anthracycline antibiotics in cancer therapy. Focus on drug resistance. *Drugs 47*, 223-258.
- Boyle, E. I., Weng, S., Gollub, J., Jin, H., Botstein, D., Cherry, J. M., and Sherlock, G. (2004). GO::TermFinder--open source software for accessing Gene Ontology information and finding significantly enriched Gene Ontology terms associated with a list of genes. *Bioinformatics 20*, 3710-3715.
- Bucheli, M., Lommel, L., and Sweder, K. (2001). The defect in transcription-coupled repair displayed by a *Saccharomyces cerevisiae* rad26 mutant is dependent on carbon source and is not associated with a lack of transcription. *Genetics 158*, 989-997.
- Butcher, R. A., and Schreiber, S. L. (2003). A small molecule suppressor of FK506 that targets the mitochondria and modulates ionic balance in *Saccharomyces cerevisiae*. *Chem Biol 10*, 521-531.
- Cao, X., Fang, L., Gibbs, S., Huang, Y., Dai, Z., Wen, P., Zheng, X., Sadee, W., and Sun, D. (2007). Glucose uptake inhibitor sensitizes cancer cells to daunorubicin and overcomes drug resistance in hypoxia. *Cancer Chemother Pharmacol 59*, 495-505.
- Cardenas, M. E., Cutler, N. S., Lorenz, M. C., Di Como, C. J., and Heitman, J. (1999). The TOR signaling cascade regulates gene expression in response to nutrients. *Genes Dev 13*, 3271-3279.
- Carroll, A. S., Bishop, A. C., DeRisi, J. L., Shokat, K. M., and O'Shea, E. K. (2001). Chemical inhibition of the Pho85 cyclin-dependent kinase reveals a role in the environmental stress response. *Proc Natl Acad Sci U S A 98*, 12578-12583.

- Causton, H. C., Ren, B., Koh, S. S., Harbison, C. T., Kanin, E., Jennings, E. G., Lee, T. I., True, H. L., Lander, E. S., and Young, R. A. (2001). Remodeling of yeast genome expression in response to environmental changes. *Mol Biol Cell* 12, 323-337.
- Clifton, D., Weinstock, S. B., and Fraenkel, D. G. (1978). Glycolysis mutants in *Saccharomyces cerevisiae*. *Genetics* 88, 1-11.
- Cox, K. H., Pinchak, A. B., and Cooper, T. G. (1999). Genome-wide transcriptional analysis in *S. cerevisiae* by mini-array membrane hybridization. *Yeast* 15, 703-713.
- Chaires, J. B. (1998). Drug--DNA interactions. *Curr Opin Struct Biol* 8, 314-320.
- Chaires, J. B. (2006). A thermodynamic signature for drug-DNA binding mode. *Arch Biochem Biophys* 453, 26-31.
- Chaires, J. B., Herrera, J. E., and Waring, M. J. (1990). Preferential binding of daunomycin to 5'ATCG and 5'ATGC sequences revealed by footprinting titration experiments. *Biochemistry* 29, 6145-6153.
- Chaires, J. B., Leng, F., Przewloka, T., Fokt, I., Ling, Y. H., Perez-Soler, R., and Priebe, W. (1997). Structure-based design of a new bisintercalating anthracycline antibiotic. *J Med Chem* 40, 261-266.
- Chaires, J. B. (1996). Molecular recognition of DNA by daunorubicin, In Advances in DNA sequence specific agents, L. Hurley, and J. B. Chaires, eds. (Greenwich, CT: JAI Press Inc.), pp. 141-167.
- Chambers, A., Packham, E. A., and Graham, I. R. (1995). Control of glycolytic gene expression in the budding yeast (*Saccharomyces cerevisiae*). *Curr Genet* 29, 1-9.
- Chan, T. F., Carvalho, J., Riles, L., and Zheng, X. F. (2000). A chemical genomics approach toward understanding the global functions of the target of rapamycin protein (TOR). *Proc Natl Acad Sci U S A* 97, 13227-13232.
- Chi, S. K., Hsu, M., Ku, W. C., Tu, C. Y., Tseng, Y. T., Lau, W. K., Yan, R. Y., Ma, J. T., and Tzeng, C. M. (2003). Synergistic effects of epoxy- and amine-silanes on microarray DNA immobilization and hybridization. *Biochem J* 374, 625-632.
- Chu, S., DeRisi, J., Eisen, M., Mulholland, J., Botstein, D., Brown, P. O., and Herskowitz, I. (1998). The transcriptional program of sporulation in budding yeast. *Science* 282, 699-705.
- Dassonneville, L., Bonjean, K., De Pauw-Gillet, M. C., Colson, P., Houssier, C., Quetin-Leclercq, J., Angenot, L., and Bailly, C. (1999). Stimulation of topoisomerase II-mediated DNA cleavage by three DNA-intercalating plant alkaloids: cryptolepine, matadine, and serpentine. *Biochemistry* 38, 7719-7726.
- Dassonneville, L., Lansiaux, A., Wattelet, A., Wattez, N., Mahieu, C., Van Miert, S., Pieters, L., and Bailly, C. (2000). Cytotoxicity and cell cycle effects of the plant

alkaloids cryptolepine and neocryptolepine: relation to drug-induced apoptosis. *Eur J Pharmacol* 409, 9-18.

Deminoff, S. J., and Santangelo, G. M. (2001). Rap1p requires Gcr1p and Gcr2p homodimers to activate ribosomal protein and glycolytic genes, respectively. *Genetics* 158, 133-143.

DeRisi, J. L., Iyer, V. R., and Brown, P. O. (1997). Exploring the metabolic and genetic control of gene expression on a genomic scale. *Science* 278, 680-686.

Dickinson, L. A., Gulizia, R. J., Trauger, J. W., Baird, E. E., Mosier, D. E., Gottesfeld, J. M., and Dervan, P. B. (1998). Inhibition of RNA polymerase II transcription in human cells by synthetic DNA-binding ligands. *Proc Natl Acad Sci U S A* 95, 12890-12895.

Drazinic, C. M., Smerge, J. B., Lopez, M. C., and Baker, H. V. (1996). Activation mechanism of the multifunctional transcription factor repressor-activator protein 1 (Rap1p). *Mol Cell Biol* 16, 3187-3196.

Duan, S., Bleibel, W. K., Huang, R. S., Shukla, S. J., Wu, X., Badner, J. A., and Dolan, M. E. (2007). Mapping genes that contribute to daunorubicin-induced cytotoxicity. *Cancer Res* 67, 5425-5433.

Emter, R., Heese-Peck, A., and Kralli, A. (2002). ERG6 and PDR5 regulate small lipophilic drug accumulation in yeast cells via distinct mechanisms. *FEBS Lett* 521, 57-61.

Flick, J. S., and Johnston, M. (1992). Analysis of URSG-mediated glucose repression of the GAL1 promoter of *Saccharomyces cerevisiae*. *Genetics* 130, 295-304.

Flint, J., Bates, G. P., Clark, K., Dorman, A., Willingham, D., Roe, B. A., Micklem, G., Higgs, D. R., and Louis, E. J. (1997). Sequence comparison of human and yeast telomeres identifies structurally distinct subtelomeric domains. *Hum Mol Genet* 6, 1305-1313.

Foufelle, F., Girard, J., and Ferre, P. (1998). Glucose regulation of gene expression. *Curr Opin Clin Nutr Metab Care* 1, 323-328.

Foury, F. (1997). Human genetic diseases: a cross-talk between man and yeast. *Gene* 195, 1-10.

Frederick, C. A., Williams, L. D., Ughetto, G., van der Marel, G. A., van Boom, J. H., Rich, A., and Wang, A. H. (1990). Structural comparison of anticancer drug-DNA complexes: adriamycin and daunomycin. *Biochemistry* 29, 2538-2549.

Gaber, R. F., Copple, D. M., Kennedy, B. K., Vidal, M., and Bard, M. (1989). The yeast gene ERG6 is required for normal membrane function but is not essential for biosynthesis of the cell-cycle-sparking sterol. *Mol Cell Biol* 9, 3447-3456.

- Gancedo, J. M. (1992). Carbon catabolite repression in yeast. *Eur J Biochem* *206*, 297-313.
- Garvie, C. W., and Wolberger, C. (2001). Recognition of specific DNA sequences. *Mol Cell* *8*, 937-946.
- Gasch, A. P., Huang, M., Metzner, S., Botstein, D., Elledge, S. J., and Brown, P. O. (2001). Genomic expression responses to DNA-damaging agents and the regulatory role of the yeast ATR homolog Mec1p. *Mol Biol Cell* *12*, 2987-3003.
- Gasch, A. P., Spellman, P. T., Kao, C. M., Carmel-Harel, O., Eisen, M. B., Storz, G., Botstein, D., and Brown, P. O. (2000). Genomic expression programs in the response of yeast cells to environmental changes. *Mol Biol Cell* *11*, 4241-4257.
- Gasch, A. P., and Werner-Washburne, M. (2002). The genomics of yeast responses to environmental stress and starvation. *Funct Integr Genomics* *2*, 181-192.
- Gewirtz, D. A. (1999). A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics adriamycin and daunorubicin. *Biochem Pharmacol* *57*, 727-741.
- Giaever, G., Chu, A. M., Ni, L., Connelly, C., Riles, L., Veronneau, S., Dow, S., Lucau-Danila, A., Anderson, K., Andre, B., et al. (2002). Functional profiling of the *Saccharomyces cerevisiae* genome. *Nature* *418*, 387-391.
- Gietz, R. D., Schiestl, R. H., Willems, A. R., and Woods, R. A. (1995). Studies on the transformation of intact yeast cells by the LiAc/SS-DNA/PEG procedure. *Yeast* *11*, 355-360.
- Giniger, E., Varnum, S. M., and Ptashne, M. (1985). Specific DNA binding of GAL4, a positive regulatory protein of yeast. *Cell* *40*, 767-774.
- Gniazdowski, M., Denny, W. A., Nelson, S. M., and Czyz, M. (2003). Transcription factors as targets for DNA-interacting drugs. *Curr Med Chem* *10*, 909-924.
- Gniazdowski, M., Denny, W. A., Nelson, S. M., and Czyz, M. (2005). Effects of anticancer drugs on transcription factor-DNA interactions. *Expert Opin Ther Targets* *9*, 471-489.
- Goffeau, A., Barrell, B. G., Bussey, H., Davis, R. W., Dujon, B., Feldmann, H., Galibert, F., Hoheisel, J. D., Jacq, C., Johnston, M., et al. (1996). Life with 6000 genes. *Science* *274*, 546, 563-547.
- Gottesfeld, J. M., Neely, L., Trauger, J. W., Baird, E. E., and Dervan, P. B. (1997). Regulation of gene expression by small molecules. *Nature* *387*, 202-205.
- Gottesfeld, J. M., Turner, J. M., and Dervan, P. B. (2000). Chemical approaches to control gene expression. *Gene Expr* *9*, 77-91.

- Gourlay, C. W., Du, W., and Ayscough, K. R. (2006). Apoptosis in yeast--mechanisms and benefits to a unicellular organism. *Mol Microbiol* *62*, 1515-1521.
- Guittat, L., Alberti, P., Rosu, F., Van Miert, S., Thetiot, E., Pieters, L., Gabelica, V., De Pauw, E., Ottaviani, A., Riou, J. F., and Mergny, J. L. (2003). Interactions of cryptolepine and neocryptolepine with unusual DNA structures. *Biochimie* *85*, 535-547.
- Hanahan, D. (1983). Studies on transformation of *Escherichia coli* with plasmids. *J Mol Biol* *166*, 557-580.
- Harbison, C. T., Gordon, D. B., Lee, T. I., Rinaldi, N. J., Macisaac, K. D., Danford, T. W., Hannett, N. M., Tagne, J. B., Reynolds, D. B., Yoo, J., *et al.* (2004). Transcriptional regulatory code of a eukaryotic genome. *Nature* *431*, 99-104.
- Hartwell, L. H. (2002). Nobel Lecture. Yeast and cancer. *Biosci Rep* *22*, 373-394.
- Hauser, N. C., Vingron, M., Scheideler, M., Krems, B., Hellmuth, K., Entian, K. D., and Hoheisel, J. D. (1998). Transcriptional profiling on all open reading frames of *Saccharomyces cerevisiae*. *Yeast* *14*, 1209-1221.
- Hemenway, C. S., and Heitman, J. (1996). Immunosuppressant target protein FKBP12 is required for P-glycoprotein function in yeast. *J Biol Chem* *271*, 18527-18534.
- Hinnebusch, A. G. (2005). Translational regulation of GCN4 and the general amino acid control of yeast. *Annu Rev Microbiol* *59*, 407-450.
- Hinnebusch, J., and Barbour, A. G. (1992). Linear- and circular-plasmid copy numbers in *Borrelia burgdorferi*. *J Bacteriol* *174*, 5251-5257.
- Holmes, D. S., and Quigley, M. (1981). A rapid boiling method for the preparation of bacterial plasmids. *Anal Biochem* *114*, 193-197.
- Horowitz, A. T., Barenholz, Y., and Gabizon, A. A. (1992). In vitro cytotoxicity of liposome-encapsulated doxorubicin: dependence on liposome composition and drug release. *Biochim Biophys Acta* *1109*, 203-209.
- Hu, G. G., Shui, X., Leng, F., Priebe, W., Chaires, J. B., and Williams, L. D. (1997). Structure of a DNA-bisdaunomycin complex. *Biochemistry* *36*, 5940-5946.
- Huang, J., Zhu, H., Haggarty, S. J., Spring, D. R., Hwang, H., Jin, F., Snyder, M., and Schreiber, S. L. (2004). Finding new components of the target of rapamycin (TOR) signaling network through chemical genetics and proteome chips. *Proc Natl Acad Sci U S A* *101*, 16594-16599.
- Huang, R. Y., Kowalski, D., Minderman, H., Gandhi, N., and Johnson, E. S. (2007). Small Ubiquitin-Related Modifier Pathway Is a Major Determinant of Doxorubicin Cytotoxicity in *Saccharomyces cerevisiae*. *Cancer Res* *67*, 765-772.

- Hughes, T. R., Marton, M. J., Jones, A. R., Roberts, C. J., Stoughton, R., Armour, C. D., Bennett, H. A., Coffey, E., Dai, H., He, Y. D., *et al.* (2000). Functional discovery via a compendium of expression profiles. *Cell* 102, 109-126.
- Iwahashi, H., Kitagawa, E., Suzuki, Y., Ueda, Y., Ishizawa, Y. H., Nobumasa, H., Kuboki, Y., Hosoda, H., and Iwahashi, Y. (2007). Evaluation of toxicity of the mycotoxin citrinin using yeast ORF DNA microarray and Oligo DNA microarray. *BMC Genomics* 8, 95.
- Jensen-Pergakes, K. L., Kennedy, M. A., Lees, N. D., Barbuch, R., Koegel, C., and Bard, M. (1998). Sequencing, disruption, and characterization of the *Candida albicans* sterol methyltransferase (ERG6) gene: drug susceptibility studies in erg6 mutants. *Antimicrob Agents Chemother* 42, 1160-1167.
- Johnston, M., and Carlson, M. (1992). Regulation of carbon and phosphate utilization. In *The Molecular and Cellular Biology of the Yeast Saccharomyces.*, Vol 2, Jones, E. W. Pringle, J. R. Broach, J. R. edn (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press).
- Jonckers, T. H., van Miert, S., Cimanga, K., Bailly, C., Colson, P., De Pauw-Gillet, M. C., van den Heuvel, H., Claeys, M., Lemiere, F., Esmans, E. L., *et al.* (2002). Synthesis, cytotoxicity, and antiplasmoidal and antitrypanosomal activity of new neocryptolepine derivatives. *J Med Chem* 45, 3497-3508.
- Karou, D., Dicko, M. H., Sanon, S., Simpore, J., and Traore, A. S. (2003). Antimalarial activity of *Sida acuta* Burm. f. (Malvaceae) and *Pterocarpus erinaceus* Poir. (Fabaceae). *J Ethnopharmacol* 89, 291-294.
- Kaur, R., and Bachhawat, A. K. (1999). The yeast multidrug resistance pump, Pdr5p, confers reduced drug resistance in erg mutants of *Saccharomyces cerevisiae*. *Microbiology* 145 (Pt 4), 809-818.
- Kelly, G. T., Liu, C., Smith, R., 3rd, Coleman, R. S., and Watanabe, C. M. (2006). Cellular effects induced by the antitumor agent azinomycin B. *Chem Biol* 13, 485-492.
- Kohrer, K., and Domdey, H. (1991). Preparation of high molecular weight RNA. *Methods Enzymol* 194, 398-405.
- Koutsoukos, A. D., Rubinstein, L. V., Faraggi, D., Simon, R. M., Kalyandrug, S., Weinstein, J. N., Kohn, K. W., and Paull, K. D. (1994). Discrimination techniques applied to the NCI in vitro anti-tumour drug screen: predicting biochemical mechanism of action. *Stat Med* 13, 719-730.
- Kubista, M., Andrade, J. M., Bengtsson, M., Forootan, A., Jonak, J., Lind, K., Sindelka, R., Sjöback, R., Sjogreen, B., Strombom, L., *et al.* (2006). The real-time polymerase chain reaction. *Mol Aspects Med* 27, 95-125.
- Kule, C., Ondrejickova, O., and Verner, K. (1994). Doxorubicin, daunorubicin, and mitoxantrone cytotoxicity in yeast. *Mol Pharmacol* 46, 1234-1240.

- Kumar, A., Larsson, O., Parodi, D., and Liang, Z. (2000). Silanized nucleic acids: a general platform for DNA immobilization. *Nucleic Acids Res* 28, E71.
- Lai, L. C., Kosorukoff, A. L., Burke, P. V., and Kwast, K. E. (2005). Dynamical remodeling of the transcriptome during short-term anaerobiosis in *Saccharomyces cerevisiae*: differential response and role of Msn2 and/or Msn4 and other factors in galactose and glucose media. *Mol Cell Biol* 25, 4075-4091.
- Lashkari, D. A., DeRisi, J. L., McCusker, J. H., Namath, A. F., Gentile, C., Hwang, S. Y., Brown, P. O., and Davis, R. W. (1997). Yeast microarrays for genome wide parallel genetic and gene expression analysis. *Proc Natl Acad Sci U S A* 94, 13057-13062.
- Lee, T. I., Rinaldi, N. J., Robert, F., Odom, D. T., Bar-Joseph, Z., Gerber, G. K., Hannett, N. M., Harbison, C. T., Thompson, C. M., Simon, I., *et al.* (2002). Transcriptional regulatory networks in *Saccharomyces cerevisiae*. *Science* 298, 799-804.
- Lee, T. I., and Young, R. A. (2000). Transcription of eukaryotic protein-coding genes. *Annu Rev Genet* 34, 77-137.
- Lemoine, F. J., Degtyareva, N. P., Lobachev, K., and Petes, T. D. (2005). Chromosomal translocations in yeast induced by low levels of DNA polymerase α model for chromosome fragile sites. *Cell* 120, 587-598.
- Leng, F., and Leno, G. H. (1997). Daunomycin disrupts nuclear assembly and the coordinate initiation of DNA replication in Xenopus egg extracts. *J Cell Biochem* 64, 476-491.
- Lerman, L. S. (1961). Structural considerations in the interaction of DNA and acridines. *J Mol Biol* 3, 18-30.
- Levy, S., Ihmels, J., Carmi, M., Weinberger, A., Friedlander, G., and Barkai, N. (2007). Strategy of transcription regulation in the budding yeast. *PLoS ONE* 2, e250.
- Liang, S. D., Marmorstein, R., Harrison, S. C., and Ptashne, M. (1996). DNA sequence preferences of GAL4 and PPR1: how a subset of Zn2 Cys6 binuclear cluster proteins recognizes DNA. *Mol Cell Biol* 16, 3773-3780.
- Lisgarten, J. N., Coll, M., Portugal, J., Wright, C. W., and Aymamí, J. (2002a). The antimalarial and cytotoxic drug cryptolepine intercalates into DNA at cytosine-cytosine sites. *Nat Struct Biol* 9, 57-60.
- Lisgarten, J. N., Pous, J., Coll, M., Wright, C. W., and Aymamí, J. (2002b). Crystallization and preliminary X-ray analysis of the antimalarial and cytotoxic alkaloid cryptolepine complexed with the DNA fragment d(CCTAGG)2. *Acta Crystallogr D Biol Crystallogr* 58, 312-313.
- Lohr, D., Venkov, P., and Zlatanova, J. (1995). Transcriptional regulation in the yeast GAL gene family: a complex genetic network. *Faseb J* 9, 777-787.

- Lopez, M. C., and Baker, H. V. (2000). Understanding the growth phenotype of the yeast *gcr1* mutant in terms of global genomic expression patterns. *J Bacteriol* *182*, 4970-4978.
- Mansilla, S., Piña, B., and Portugal, J. (2003). Daunorubicin-induced variations in gene transcription: commitment to proliferation arrest, senescence and apoptosis. *Biochem J* *372*, 703-711.
- Mansilla, S., and Portugal, J. (2002). Occurrence of DNA sequences specifically recognized by drugs in human promoters. *J Biomol Struct Dyn* *19*, 669-679.
- Mansilla, S., Priebe, W., and Portugal, J. (2004). Sp1-targeted inhibition of gene transcription by WP631 in transfected lymphocytes. *Biochemistry* *43*, 7584-7592.
- Mansilla, S., Priebe, W., and Portugal, J. (2006). Mitotic catastrophe results in cell death by caspase-dependent and caspase-independent mechanisms. *Cell Cycle* *5*, 53-60.
- Mansilla, S., Rojas, M., Bataller, M., Priebe, W., and Portugal, J. (2007). Circumvention of the multidrug-resistance protein (MRP-1) by an antitumor drug through specific inhibition of gene transcription in breast tumor cells. *Biochem Pharmacol* *73*, 934-942.
- Marín, S., Mansilla, S., Garcia-Reyero, N., Rojas, M., Portugal, J., and Piña, B. (2002). Promoter-specific inhibition of transcription by daunorubicin in *Saccharomyces cerevisiae*. *Biochem J* *368*, 131-136.
- Markovich, S., Yekutiel, A., Shalit, I., Shadkchan, Y., and Osherov, N. (2004). Genomic approach to identification of mutations affecting caspofungin susceptibility in *Saccharomyces cerevisiae*. *Antimicrob Agents Chemother* *48*, 3871-3876.
- Martín, B., Vaquero, A., Priebe, W., and Portugal, J. (1999). Bisantrenacycline WP631 inhibits basal and Sp1-activated transcription initiation in vitro. *Nucleic Acids Res* *27*, 3402-3409.
- Marton, M. J., DeRisi, J. L., Bennett, H. A., Iyer, V. R., Meyer, M. R., Roberts, C. J., Stoughton, R., Burchard, J., Slade, D., Dai, H., *et al.* (1998). Drug target validation and identification of secondary drug target effects using DNA microarrays. *Nat Med* *4*, 1293-1301.
- Matys, V., Fricke, E., Geffers, R., Gossling, E., Haubrock, M., Hehl, R., Hornischer, K., Karas, D., Kel, A. E., Kel-Margoulis, O. V., *et al.* (2003). TRANSFAC: transcriptional regulation, from patterns to profiles. *Nucleic Acids Res* *31*, 374-378.
- Meneghini, M. D., Wu, M., and Madhani, H. D. (2003). Conserved histone variant H2A.Z protects euchromatin from the ectopic spread of silent heterochromatin. *Cell* *112*, 725-736.
- Minard, K. I., and McAlister-Henn, L. (2001). Antioxidant function of cytosolic sources of NADPH in yeast. *Free Radic Biol Med* *31*, 832-843.

- Minotti, G., Menna, P., Salvatorelli, E., Cairo, G., and Gianni, L. (2004). Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol Rev* 56, 185-229.
- Mnaimneh, S., Davierwala, A. P., Haynes, J., Moffat, J., Peng, W. T., Zhang, W., Yang, X., Pootoolal, J., Chua, G., Lopez, A., *et al.* (2004). Exploration of essential gene functions via titratable promoter alleles. *Cell* 118, 31-44.
- Mukhopadhyay, K., Kohli, A., and Prasad, R. (2002). Drug susceptibilities of yeast cells are affected by membrane lipid composition. *Antimicrob Agents Chemother* 46, 3695-3705.
- Natarajan, K., Meyer, M. R., Jackson, B. M., Slade, D., Roberts, C., Hinnebusch, A. G., and Marton, M. J. (2001). Transcriptional profiling shows that Gcn4p is a master regulator of gene expression during amino acid starvation in yeast. *Mol Cell Biol* 21, 4347-4368.
- Nehil, M. T., Tamble, C. M., Combs, D. J., Kellogg, D. R., and Lokey, R. S. (2007). Uncovering genetic relationships using small molecules that selectively target yeast cell cycle mutants. *Chem Biol Drug Des* 69, 258-264.
- Neidle, S. (2001). DNA minor-groove recognition by small molecules. *Nat Prod Rep* 18, 291-309.
- Nelson, S. M., Ferguson, L. R., and Denny, W. A. (2004). DNA and the chromosome - varied targets for chemotherapy. *Cell Chromosome* 3, 2.
- Nitiss, J., and Wang, J. C. (1988). DNA topoisomerase-targeting antitumor drugs can be studied in yeast. *Proc Natl Acad Sci U S A* 85, 7501-7505.
- Nitiss, J. L., Liu, Y. X., Harbury, P., Jannatipour, M., Wasserman, R., and Wang, J. C. (1992). Amsacrine and etoposide hypersensitivity of yeast cells overexpressing DNA topoisomerase II. *Cancer Res* 52, 4467-4472.
- Noamesi, B. K., Larsson, B. S., Laryea, D. L., and Ullberg, S. (1991). Whole-body autoradiographic study on the distribution of 3H-cryptolepine in mice. *Arch Int Pharmacodyn Ther* 313, 5-14.
- Onyeibor, O., Croft, S. L., Dodson, H. I., Feiz-Haddad, M., Kendrick, H., Millington, N. J., Parapini, S., Phillips, R. M., Seville, S., Shnyder, S. D., *et al.* (2005). Synthesis of some cryptolepine analogues, assessment of their antimalarial and cytotoxic activities, and consideration of their antimalarial mode of action. *J Med Chem* 48, 2701-2709.
- Ooi, S. L., Pan, X., Peyser, B. D., Ye, P., Meluh, P. B., Yuan, D. S., Irizarry, R. A., Bader, J. S., Spencer, F. A., and Boeke, J. D. (2006). Global synthetic-lethality analysis and yeast functional profiling. *Trends Genet* 22, 56-63.
- Outeiro, T. F., and Giorgini, F. (2006). Yeast as a drug discovery platform in Huntington's and Parkinson's diseases. *Biotechnol J* 1, 258-269.

- Palecek, S. P., Parikh, A. S., Huh, J. H., and Kron, S. J. (2002). Depression of *Saccharomyces cerevisiae* invasive growth on non-glucose carbon sources requires the Snf1 kinase. *Mol Microbiol* 45, 453-469.
- Pan, X., and Heitman, J. (2000). Sok2 regulates yeast pseudohyphal differentiation via a transcription factor cascade that regulates cell-cell adhesion. *Mol Cell Biol* 20, 8364-8372.
- Parsons, A. B., Brost, R. L., Ding, H., Li, Z., Zhang, C., Sheikh, B., Brown, G. W., Kane, P. M., Hughes, T. R., and Boone, C. (2004). Integration of chemical-genetic and genetic interaction data links bioactive compounds to cellular target pathways. *Nat Biotechnol* 22, 62-69.
- Parsons, A. B., Geyer, R., Hughes, T. R., and Boone, C. (2003). Yeast genomics and proteomics in drug discovery and target validation. *Prog Cell Cycle Res* 5, 159-166.
- Pellicano, H., Martin, D. S., Xu, R. H., and Huang, P. (2006). Glycolysis inhibition for anticancer treatment. *Oncogene* 25, 4633-4646.
- Perego, P., Corna, E., De Cesare, M., Gatti, L., Polizzi, D., Pratesi, G., Supino, R., and Zunino, F. (2001). Role of apoptosis and apoptosis-related genes in cellular response and antitumor efficacy of anthracyclines. *Curr Med Chem* 8, 31-37.
- Perkins, E., Sun, D., Nguyen, A., Tulac, S., Francesco, M., Tavana, H., Nguyen, H., Tugendreich, S., Barthmaier, P., Couto, J., *et al.* (2001). Novel inhibitors of poly(ADP-ribose) polymerase/PARP1 and PARP2 identified using a cell-based screen in yeast. *Cancer Res* 61, 4175-4183.
- Piña, B. (2000). Many Ways of Transcriptional Regulation in Yeast. *Food technology and biotechnology* 38, 253–262.
- Portugal, J., Martín, B., Vaquero, A., Ferrer, N., Villamarín, S., and Priebe, W. (2001). Analysis of the effects of daunorubicin and WP631 on transcription. *Curr Med Chem* 8, 1-8.
- Priebe, W., Fokt, I., Przewloka, T., Chaires, J. B., Portugal, J., and Trent, J. O. (2001). Exploiting anthracycline scaffold for designing DNA-targeting agents. *Methods Enzymol* 340, 529-555.
- Roberts, C. J., Nelson, B., Marton, M. J., Stoughton, R., Meyer, M. R., Bennett, H. A., He, Y. D., Dai, H., Walker, W. L., Hughes, T. R., *et al.* (2000). Signaling and circuitry of multiple MAPK pathways revealed by a matrix of global gene expression profiles. *Science* 287, 873-880.
- Sadowski, I., Costa, C., and Dhanawansa, R. (1996). Phosphorylation of Ga14p at a single C-terminal residue is necessary for galactose-inducible transcription. *Mol Cell Biol* 16, 4879-4887.
- Saffran, W. A., Ahmed, S., Bellevue, S., Pereira, G., Patrick, T., Sanchez, W., Thomas, S., Alberti, M., and Hearst, J. E. (2004). DNA repair defects channel interstrand DNA

cross-links into alternate recombinational and error-prone repair pathways. *J Biol Chem* 279, 36462-36469.

Saiki, R. K., Gelfand, D. H., Stoffel, S., Scharf, S. J., Higuchi, R., Horn, G. T., Mullis, K. B., and Erlich, H. A. (1988). Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase. *Science* 239, 487-491.

Sambrook, J., Fritsch, E. F., and Maniatis, T. (1989). Molecular cloning (Cold Spring Harbor: Cold Spring Harbor Laboratory Press).

Santangelo, G. M., and Tornow, J. (1990). Efficient transcription of the glycolytic gene ADH1 and three translational component genes requires the GCR1 product, which can act through TUF/GRF/RAP binding sites. *Mol Cell Biol* 10, 859-862.

Sasaki, H., and Uemura, H. (2005). Influence of low glycolytic activities in gcr1 and gcr2 mutants on the expression of other metabolic pathway genes in *Saccharomyces cerevisiae*. *Yeast* 22, 111-127.

Savoie, C. J., Aburatani, S., Watanabe, S., Eguchi, Y., Muta, S., Imoto, S., Miyano, S., Kuhara, S., and Tashiro, K. (2003). Use of gene networks from full genome microarray libraries to identify functionally relevant drug-affected genes and gene regulation cascades. *DNA Res* 10, 19-25.

Sawer, I. K., Berry, M. I., and Ford, J. L. (2005). The killing effect of cryptolepine on *Staphylococcus aureus*. *Lett Appl Microbiol* 40, 24-29.

Schade, B., Jansen, G., Whiteway, M., Entian, K. D., and Thomas, D. Y. (2004). Cold adaptation in budding yeast. *Mol Biol Cell* 15, 5492-5502.

Schena, M., Shalon, D., Davis, R. W., and Brown, P. O. (1995). Quantitative monitoring of gene expression patterns with a complementary DNA microarray. *Science* 270, 467-470.

Schulze, A., and Downward, J. (2001). Navigating gene expression using microarrays--a technology review. *Nat Cell Biol* 3, E190-195.

Seville, S., Phillips, R. M., Shnyder, S. D., and Wright, C. W. (2007). Synthesis of cryptolepine analogues as potential bioreducible anticancer agents. *Bioorg Med Chem*.

Shalon, D., Smith, S. J., and Brown, P. O. (1996). A DNA microarray system for analyzing complex DNA samples using two-color fluorescent probe hybridization. *Genome Res* 6, 639-645.

Shannon, M. F., and Rao, S. (2002). Transcription. Of chips and ChIPs. *Science* 296, 666-669.

Sharma, S. C. (2006). Implications of sterol structure for membrane lipid composition, fluidity and phospholipid asymmetry in *Saccharomyces cerevisiae*. *FEMS Yeast Res* 6, 1047-1051.

- Shaw, R. J. (2006). Glucose metabolism and cancer. *Curr Opin Cell Biol 18*, 598-608.
- Shoemaker, R. H., Abbott, B. J., Macdonald, M. M., Mayo, J. G., Venditti, J. M., and Wolpert-DeFilipps, M. K. (1983). Use of the KB cell line for in vitro cytotoxicity assays. *Cancer Treat Rep 67*, 97.
- Shrivastav, S., Bonar, R. A., Stone, K. R., and Paulson, D. F. (1980). An in vitro assay procedure to test chemotherapeutic drugs on cells from human solid tumors. *Cancer Res 40*, 4438-4442.
- Sikorski, R. S., and Hieter, P. (1989). A system of shuttle vectors and yeast host strains designed for efficient manipulation of DNA in *Saccharomyces cerevisiae*. *Genetics 122*, 19-27.
- Simon, J. A., and Bedalov, A. (2004). Yeast as a model system for anticancer drug discovery. *Nat Rev Cancer 4*, 481-492.
- Slekar, K. H., Kosman, D. J., and Culotta, V. C. (1996). The yeast copper/zinc superoxide dismutase and the pentose phosphate pathway play overlapping roles in oxidative stress protection. *J Biol Chem 271*, 28831-28836.
- Taylor, A., Webster, K. A., Gustafson, T. A., and Kedes, L. (1997). The anti-cancer agent distamycin A displaces essential transcription factors and selectively inhibits myogenic differentiation. *Mol Cell Biochem 169*, 61-72.
- Teixeira, M. C., Monteiro, P., Jain, P., Tenreiro, S., Fernandes, A. R., Mira, N. P., Alenquer, M., Freitas, A. T., Oliveira, A. L., and Sa-Correia, I. (2006). The YEASTRACT database: a tool for the analysis of transcription regulatory associations in *Saccharomyces cerevisiae*. *Nucleic Acids Res 34*, D446-451.
- Tong, A. H., Evangelista, M., Parsons, A. B., Xu, H., Bader, G. D., Page, N., Robinson, M., Raghibizadeh, S., Hogue, C. W., Bussey, H., et al. (2001). Systematic genetic analysis with ordered arrays of yeast deletion mutants. *Science 294*, 2364-2368.
- Tong, A. H., Lesage, G., Bader, G. D., Ding, H., Xu, H., Xin, X., Young, J., Berriz, G. F., Brost, R. L., Chang, M., et al. (2004). Global mapping of the yeast genetic interaction network. *Science 303*, 808-813.
- Tornow, J., Zeng, X., Gao, W., and Santangelo, G. M. (1993). GCR1, a transcriptional activator in *Saccharomyces cerevisiae*, complexes with RAP1 and can function without its DNA binding domain. *Embo J 12*, 2431-2437.
- Travers, K. J., Patil, C. K., Wodicka, L., Lockhart, D. J., Weissman, J. S., and Walter, P. (2000). Functional and genomic analyses reveal an essential coordination between the unfolded protein response and ER-associated degradation. *Cell 101*, 249-258.
- Tugendreich, S., Perkins, E., Couto, J., Barthmaier, P., Sun, D., Tang, S., Tulac, S., Nguyen, A., Yeh, E., Mays, A., et al. (2001). A streamlined process to phenotypically profile heterologous cDNAs in parallel using yeast cell-based assays. *Genome Res 11*, 1899-1912.

- Turkel, S., Liao, X. B., and Farabaugh, P. J. (1997). GCR1-dependent transcriptional activation of yeast retrotransposon Ty2-917. *Yeast 13*, 917-930.
- Uemura, H., and Fraenkel, D. G. (1990). gcr2, a new mutation affecting glycolytic gene expression in *Saccharomyces cerevisiae*. *Mol Cell Biol 10*, 6389-6396.
- Uemura, H., and Jigami, Y. (1992). Role of GCR2 in transcriptional activation of yeast glycolytic genes. *Mol Cell Biol 12*, 3834-3842.
- Valentini, L., Nicolella, V., Vannini, E., Menozzi, M., Penco, S., and Arcamone, F. (1985). Association of anthracycline derivatives with DNA: a fluorescence study. *Farmaco [Sci] 40*, 377-390.
- van Hal, N. L., Vorst, O., van Houwelingen, A. M., Kok, E. J., Peijnenburg, A., Aharoni, A., van Tunen, A. J., and Keijer, J. (2000). The application of DNA microarrays in gene expression analysis. *J Biotechnol 78*, 271-280.
- Van Miert, S., Jonckers, T., Cimanga, K., Maes, L., Maes, B., Lemiere, G., Dommisse, R., Vlietinck, A., and Pieters, L. (2004). In vitro inhibition of beta-haematin formation, DNA interactions, antiplasmoidal activity, and cytotoxicity of synthetic neocryptolepine derivatives. *Exp Parasitol 108*, 163-168.
- Velculescu, V. E., Zhang, L., Zhou, W., Vogelstein, J., Basrai, M. A., Bassett, D. E., Jr., Hieter, P., Vogelstein, B., and Kinzler, K. W. (1997). Characterization of the yeast transcriptome. *Cell 88*, 243-251.
- Villamarín, S., Ferrer-Miralles, N., Mansilla, S., Priebe, W., and Portugal, J. (2002). Induction of G(2)/M arrest and inhibition of c-myc and p53 transcription by WP631 in Jurkat T lymphocytes. *Biochem Pharmacol 63*, 1251-1258.
- Waring, M. J. (1981). DNA modification and cancer. *Annu Rev Biochem 50*, 159-192.
- Warner, J. R. (1999). The economics of ribosome biosynthesis in yeast. *Trends Biochem Sci 24*, 437-440.
- Weiss, R. B. (1992). The anthracyclines: will we ever find a better doxorubicin? *Semin Oncol 19*, 670-686.
- Wemmer, D. E., and Dervan, P. B. (1997). Targeting the minor groove of DNA. *Curr Opin Struct Biol 7*, 355-361.
- Winzeler, E. A., Shoemaker, D. D., Astromoff, A., Liang, H., Anderson, K., Andre, B., Bangham, R., Benito, R., Boeke, J. D., Bussey, H., *et al.* (1999). Functional characterization of the *S. cerevisiae* genome by gene deletion and parallel analysis. *Science 285*, 901-906.
- Wright, C. W., Addae-Kyereme, J., Breen, A. G., Brown, J. E., Cox, M. F., Croft, S. L., Gokcek, Y., Kendrick, H., Phillips, R. M., and Pollet, P. L. (2001). Synthesis and evaluation of cryptolepine analogues for their potential as new antimalarial agents. *J Med Chem 44*, 3187-3194.

- Wyrick, J. J., Holstege, F. C., Jennings, E. G., Causton, H. C., Shore, D., Grunstein, M., Lander, E. S., and Young, R. A. (1999). Chromosomal landscape of nucleosome-dependent gene expression and silencing in yeast. *Nature* *402*, 418-421.
- Xie, Y., and Varshavsky, A. (2001). RPN4 is a ligand, substrate, and transcriptional regulator of the 26S proteasome: a negative feedback circuit. *Proc Natl Acad Sci U S A* *98*, 3056-3061.
- Xu, R. H., Pelicano, H., Zhou, Y., Carew, J. S., Feng, L., Bhalla, K. N., Keating, M. J., and Huang, P. (2005). Inhibition of glycolysis in cancer cells: a novel strategy to overcome drug resistance associated with mitochondrial respiratory defect and hypoxia. *Cancer Res* *65*, 613-621.
- Yin, Z., Wilson, S., Hauser, N. C., Tournu, H., Hoheisel, J. D., and Brown, A. J. (2003). Glucose triggers different global responses in yeast, depending on the strength of the signal, and transiently stabilizes ribosomal protein mRNAs. *Mol Microbiol* *48*, 713-724.
- Young, R. A. (2000). Biomedical discovery with DNA arrays. *Cell* *102*, 9-15.
- Zacharias, M. (2006). Minor groove deformability of DNA: a molecular dynamics free energy simulation study. *Biophys J* *91*, 882-891.
- Zammattéo, N., Jeanmart, L., Hamels, S., Courtois, S., Louette, P., Hevesi, L., and Remacle, J. (2000). Comparison between different strategies of covalent attachment of DNA to glass surfaces to build DNA microarrays. *Anal Biochem* *280*, 143-150.
- Zeng, X., Deminoff, S. J., and Santangelo, G. M. (1997). Specialized Rap1p/Gcr1p transcriptional activation through Gcr1p DNA contacts requires Gcr2p, as does hyperphosphorylation of Gcr1p. *Genetics* *147*, 493-505.
- Zhao, Y., McIntosh, K. B., Rudra, D., Schawalder, S., Shore, D., and Warner, J. R. (2006). Fine-structure analysis of ribosomal protein gene transcription. *Mol Cell Biol* *26*, 4853-4862.
- Zhu, H., and Gooderham, N. J. (2006). Mechanisms of induction of cell cycle arrest and cell death by cryptolepine in human lung adenocarcinoma a549 cells. *Toxicol Sci* *91*, 132-139.