

### Supplemental references

- S1. Soliman, M., Kaplan, E., Fisfalen, M.E., Okamoto, Y., and DeGroot, L.J. 1995. T-cell reactivity to recombinant human thyrotropin receptor extracellular domain and thyroglobulin in patients with autoimmune and nonautoimmune thyroid diseases. *J Clin Endocrinol Metab* 80:206-213.
- S2. Martin, A., Barbesino, G., and Davies, T.F. 1999. T-cell receptors and autoimmune thyroid disease--signposts for T-cell-antigen driven diseases. *Int Rev Immunol* 18:111-140.
- S3. Adams, D.D., and Purves, H.D. 1956. Abnormal responses in the assay of thyrotropins. *Proc Univ Otago Sch Med* 34:11-12.
- S4. Kriss, J., Pleshakov, V., and Chien, J.R. 1964. Isolation and identification of the long acting thyroid stimulator and its relation to hyperthyroidism and circumscribed pretibial myxedema. *J Clin Endocrinol Metab* 24:1005-1028.
- S5. Rees Smith, B., McLachlan, S.M., and Furmaniak, J. 1988. Autoantibodies to the thyrotropin receptor. *Endocr Rev* 9:106-121.
- S6. Adams, D.D., Fastier, F.N., Howie, J.B., Kennedy, T.H., Kilpatrick, J.A., and Stewart, R.D. 1974. Stimulation of the human thyroid by infusions of plasma containing LATS protector. *J Clin Endocrinol Metab* 39:826-832.
- S7. Davies, T.F., Vlase, H., and Kita, M. 1999. The search for an animal model for Graves' disease. In *The Decade of Autoimmunity*. Y. Shoenfeld, editor. Amsterdam; New York: Elsevier Science. 43-50.
- S8. Ludgate, M. 2000. Animal models of Graves' disease. *Eur J Endocrinol* 142:1-8.
- S9. Costagliola, S., Many, M.C., Stalmans-Falys, M., Tonacchera, M., Vassart, G., and Ludgate, M. 1994. Recombinant thyrotropin receptor and the induction of autoimmune thyroid disease in BALB/c mice: a new animal model. *Endocrinology* 135:2150-2159.
- S10. Vlase, H., Weiss, M., Graves, P.N., and Davies, T.F. 1998. Characterization of the murine immune response to the murine TSH receptor ectodomain: induction of hypothyroidism and TSH receptor antibodies. *Clin Exp Immunol* 113:111-118.

- S11. Shimojo, N., Kohno, Y., Yamaguchi, K., Kikuoka, S., Hoshioka, A., Niimi, H., Hirai, A., Tamura, Y., Saito, Y., Kohn, L.D., et al. 1996. Induction of Graves-like disease in mice by immunization with fibroblasts transfected with the thyrotropin receptor and a class II molecule. *Proc Natl Acad Sci U S A* 93:11074-11079.
- S12. Kita, M., Ahmad, L., Marians, R.C., Vlase, H., Unger, P., Graves, P.N., and Davies, T.F. 1999. Regulation and transfer of a murine model of thyrotropin receptor antibody mediated Graves' disease. *Endocrinology* 140:1392-1398.
- S13. Kikuoka, S., Shimojo, N., Yamaguchi, K.I., Watanabe, Y., Hoshioka, A., Hirai, A., Saito, Y., Tahara, K., Kohn, L.D., Maruyama, N., et al. 1998. The formation of thyrotropin receptor (TSHR) antibodies in a Graves' animal model requires the N-terminal segment of the TSHR extracellular domain. *Endocrinology* 139:1891-1898.
- S14. Costagliola, S., Rodien, P., Many, M.C., Ludgate, M., and Vassart, G. 1998. Genetic immunization against the human thyrotropin receptor causes thyroiditis and allows production of monoclonal antibodies recognizing the native receptor. *J Immunol* 160:1458-1465.
- S15. Costagliola, S., Many, M.C., Deneff, J.F., Pohlenz, J., Refetoff, S., and Vassart, G. 2000. Genetic immunization of outbred mice with thyrotropin receptor cDNA provides a model of Graves' disease. *J Clin Invest* 105:803-811.
- S16. Nagayama, Y., Kita-Furuyama, M., Ando, T., Nakao, K., Mizuguchi, H., Hayakawa, T., Eguchi, K., and Niwa, M. 2002. A novel murine model of Graves' hyperthyroidism with intramuscular injection of adenovirus expressing the thyrotropin receptor. *J Immunol* 168:2789-2794.
- S17. Chen, C.R., Pichurin, P., Nagayama, Y., Latorofa, F., Rapoport, B., and McLachlan, S.M. 2003. The thyrotropin receptor autoantigen in Graves' disease is the culprit as well as the victim. *J Clin Invest* 111:1897-1904.
- S18. Weetman, A.P., Yateman, M.E., Ealey, P.A., Black, C.M., Reimer, C.B., Williams, R.C., Jr., Shine, B., and Marshall, N.J. 1990. Thyroid-stimulating antibody activity between different immunoglobulin G subclasses. *J Clin Invest* 86:723-727.
- S19. Nagayama, Y., Mizuguchi, H., Hayakawa, T., Niwa, M., McLachlan, S.M., and Rapoport, B. 2003. Prevention of autoantibody-mediated Graves'-like hyperthyroidism in mice with IL-4, a Th2 cytokine. *J Immunol* 170:3522-3527.

- S20. Sanders, J., Evans, M., Premawardhana, L.D., Depraetere, H., Jeffreys, J., Richards, T., Furmaniak, J., and Rees Smith, B. 2003. Human monoclonal thyroid stimulating autoantibody. *Lancet* 362:126-128.
- S21. Ando, T., Latif, R., Pritsker, A., Moran, T., Nagayama, Y., and Davies, T.F. 2002. A monoclonal thyroid-stimulating antibody. *J Clin Invest* 110:1667-1674.
- S22. Sanders, J., Jeffreys, J., Depraetere, H., Richards, T., Evans, M., Kiddie, A., Brereton, K., Groenen, M., Oda, Y., Furmaniak, J., et al. 2002. Thyroid-stimulating monoclonal antibodies. *Thyroid* 12:1043-1050.
- S23. Ando, T., Latif, R., Daniel, S., Eguchi, K., and Davies, T.F. 2004. Dissecting linear and conformational epitopes on the native thyrotropin receptor. *Endocrinology* 145:5185-5193.
- S24. Costagliola, S., Bonomi, M., Morgenthaler, N.G., Van Durme, J., Panneels, V., Refetoff, S., and Vassart, G. 2004. Delineation of the discontinuous-conformational epitope of a monoclonal antibody displaying full in vitro and in vivo thyrotropin activity. *Mol Endocrinol* 18:3020-3034.
- S25. Chazenbalk, G.D., Pichurin, P., Chen, C.R., Latrofa, F., Johnstone, A.P., McLachlan, S.M., and Rapoport, B. 2002. Thyroid-stimulating autoantibodies in Graves disease preferentially recognize the free A subunit, not the thyrotropin holoreceptor. *J Clin Invest* 110:209-217.
- S26. Vassart, G., and Costagliola, S. 2004. A physiological role for the posttranslational cleavage of the thyrotropin receptor? *Endocrinology* 145:1-3.
- S27. Kraiem, Z., Lahat, N., Glaser, B., Baron, E., Sadeh, O., and Sheinfeld, M. 1987. Thyrotropin receptor blocking antibodies: incidence, characterization, and in-vitro synthesis. *Clin Endocrinol (Oxf)* 27:409-421.
- S28. Zakarija, M., De Forteza, R., McKenzie, J.M., and Ghandur-Mnaymneh, L. 1994. Characteristics and clinical correlates of a novel thyroid-stimulating autoantibody. *Autoimmunity* 19:31-37.
- S29. Mukhtar, E.D., Smith, B.R., Pyle, G.A., Hall, R., and Vice, P. 1975. Relation of thyroid-stimulating immunoglobulins to thyroid function and effects of surgery, radioiodine, and antithyroid drugs. *Lancet* 1:713-715.
- S30. Endo, K., Kasagi, K., Konishi, J., Ikeburo, K., Okuno, T., Takeda, Y.,

Mori, T., and Torizuka, K. 1978. Detection and properties of TSH-binding inhibitor immunoglobulin in patients with Graves' disease and Hashimoto's thyroiditis. *J Clin Endocrinol Metab* 46:734-739.

S31. Tamai, H., Kasagi, K., Takaichi, Y., Takamatsu, J., Komaki, G., Matsubayashi, S., Konishi, J., Kuma, K., Kumagai, L.F., and Nagataki, S. 1989. Development of spontaneous hypothyroidism in patients with Graves' disease treated with antithyroidal drugs: clinical, immunological, and histological findings in 26 patients. *J Clin Endocrinol Metab* 69:49-53.

S32. Matsuura, N., Yamada, Y., and Nohata, Y. 1980. Familial neonatal hypothyroidism due to maternal TSH-binding inhibiting immunoglobulins. *N Engl J Med* 303:738-741.

S33. Minich, W.B., Lenzner, C., and Morgenthaler, N.G. 2004. Antibodies to TSH-receptor in thyroid autoimmune disease interact with monoclonal antibodies whose epitopes are broadly distributed on the receptor. *Clin Exp Immunol* 136:129-136.

S34. Ando, T., Latif, R., Daniel, S., Eguchi, K., and Davies, T.F. 2004. Dissecting linear and conformational epitopes on the native thyrotropin receptor. *Endocrinology*:in press.

S35. Tonacchera, M., Costagliola, S., Cetani, F., Ducobu, J., Stordeur, P., Vassart, G., and Ludgate, M. 1996. Patient with monoclonal gammopathy, thyrotoxicosis, pretibial edema and thyroid-associated ophthalmopathy; demonstration of direct binding of autoantibodies to the thyrotropin receptor. *Eur J Endocrinol* 134:97-103.

S36. Schwarz-Lauer, L., Chazenbalk, G.D., McLachlan, S.M., Ochi, Y., Nagayama, Y., and Rapoport, B. 2002. Evidence for a simplified view of autoantibody interactions with the thyrotropin receptor. *Thyroid* 12:115-120.

S37. Schwarz-Lauer, L., Pichurin, P.N., Chen, C.R., Nagayama, Y., Paras, C., Morris, J.C., Rapoport, B., and McLachlan, S.M. 2003. The cysteine-rich amino terminus of the thyrotropin receptor is the immunodominant linear antibody epitope in mice immunized using naked deoxyribonucleic acid or adenovirus vectors. *Endocrinology* 144:1718-1725.

S38. Takao Ando, R.L.a.T.F.D. 2005. Maintaining Graves' disease-TSH receptor autoantibodies lengthen the surface half-life of the TSH receptor. *Annual*

*Meeting of the Endocrine Society.*

- S39. Smith, B.R., Bolton, J., Young, S., Collyer, A., Weeden, A., Bradbury, J., Weightman, D., Perros, P., Sanders, J., and Furmaniak, J. 2004. A new assay for thyrotropin receptor autoantibodies. *Thyroid* 14:830-835.
- S40. Davies, T.F., Roti, E., Braverman, L.E., and Degroot, L.J. 1998. Thyroid controversy-stimulating antibodies. *J Clin Endocrinol Metab* 83:3777-3785.
- S41. Smith, B.R., and Hall, R. 1974. Thyroid-stimulating immunoglobulins in Graves' disease. *Lancet* 2:427-431.
- S42. Shewring, G., and Smith, B.R. 1982. An improved radioreceptor assay for TSH receptor antibodies. *Clin Endocrinol (Oxf)* 17:409-417.
- S43. Smith, B.R. 2001. Thyroid autoantibodies. *Scand J Clin Lab Invest Suppl* 235:45-52.
- S44. Costagliola, S., Morgenthaler, N.G., Hoermann, R., Badenhoop, K., Struck, J., Freitag, D., Poertl, S., Weglohner, W., Hollidt, J.M., Quadbeck, B., et al. 1999. Second generation assay for thyrotropin receptor antibodies has superior diagnostic sensitivity for Graves' disease. *J Clin Endocrinol Metab* 84:90-97.
- S45. Bolton, J., Sanders, J., Oda, Y., Chapman, C., Konno, R., Furmaniak, J., and Rees Smith, B. 1999. Measurement of thyroid-stimulating hormone receptor autoantibodies by ELISA. *Clin Chem* 45:2285-2287.
- S46. Endo, K., Borges, M., Amir, S., and Ingbar, S.H. 1982. Preparation of <sup>125</sup>I-labeled receptor-purified Graves' immunoglobulins: properties of their binding to human thyroid membranes. *J Clin Endocrinol Metab* 55:566-576.
- S47. Davies, T.F., and Larsen, P.R. 2003. Thyrotoxicosis. In *Williams textbook of Endocrinology*: Saunders. 374-422.
- S48. Weetman, A.P. 1994. The immunomodulatory effects of antithyroid drugs. *Thyroid* 4:145-146.
- S49. Volpe, R., Karlsson, A., Jansson, R., and Dahlberg, P.A. 1986. Evidence that antithyroid drugs induce remissions in Graves' disease by modulating thyroid cellular activity. *Clin Endocrinol (Oxf)* 25:453-462.
- S50. Davies, T.F., Yeo, P.P., Evered, D.C., Clark, F., Smith, B.R., and Hall, R. 1977. Value of thyroid-stimulating-antibody determinations in predicting short-term

thyrotoxic relapse in Graves' disease. *Lancet* 1:1181-1182.

S51. Michelangeli, V., Poon, C., Taft, J., Newnham, H., Topliss, D., and Colman, P. 1998. The prognostic value of thyrotropin receptor antibody measurement in the early stages of treatment of Graves' disease with antithyroid drugs. *Thyroid* 8:119-124.

S52. Feldt-Rasmussen, U., Schleusener, H., and Carayon, P. 1994. Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long term remission after medical therapy of Graves' disease. *J Clin Endocrinol Metab* 78:98-102.

S53. Rees Smith, B., Bolton, J., Young, S., Collyer, A., Weeden, A., Bradbury, J., Weightman, D., Perros, P., Sanders, J., and Furmaniak, J. 2004. A new assay for TSH receptor autoantibodies. *Thyroid* 14:in press.

S54. Jaume, J.C., Kakinuma, A., Chazenbalk, G.D., Rapoport, B., and McLachlan, S.M. 1997. Thyrotropin receptor autoantibodies in serum are present at much lower levels than thyroid peroxidase autoantibodies: analysis by flow cytometry. *J Clin Endocrinol Metab* 82:500-507.

S55. McGregor, A.M., McLachlan, S.M., Smith, B.R., and Hall, R. 1979. Effect of irradiation on thyroid-autoantibody production. *Lancet* 2:442-444.

S56. Pacini, F., Vorontsova, T., Molinaro, E., Kuchinskaya, E., Agate, L., Shavrova, E., Astachova, L., Chiovato, L., and Pinchera, A. 1998. Prevalence of thyroid autoantibodies in children and adolescents from Belarus exposed to the Chernobyl radioactive fallout. *Lancet* 352:763-766.

S57. DeGroot, L.J. 1993. Effects of irradiation on the thyroid gland. *Endocrinol Metab Clin North Am* 22:607-615.

S58. Spitzweg, C., Joba, W., and Heufelder, A.E. 1999. Expression of thyroid-related genes in human thymus. *Thyroid* 9:133-141.

S59. Prabhakar, B.S., Bahn, R.S., and Smith, T.J. 2003. Current perspective on the pathogenesis of Graves' disease and ophthalmopathy. *Endocr Rev* 24:802-835.

S60. Heufelder, A.E. 2000. Pathogenesis of ophthalmopathy in autoimmune thyroid disease. *Rev Endocr Metab Disord* 1:87-95.

S61. Bahn, R.S. 2003. Pathophysiology of Graves' ophthalmopathy: the cycle of disease. *J Clin Endocrinol Metab* 88:1939-1946.

- S62. Paschke, R., and Ludgate, M. 1997. Mechanisms of disease: The thyrotropin receptor in thyroid diseases. *N Engl J Med* 337:1675-1681.
- S63. Chabaud, O., and Lissitzky, S. 1977. Thyrotropin-specific binding to human peripheral blood monocytes and polymorphonuclear leukocytes. *Mol Cell Endocrinol* 7:79-87.
- S64. Davies, T.F., Teng, C.S., McLachlan, S.M., Smith, B.R., and Hall, R. 1978. Thyrotropin receptors in adipose tissue, retro-orbital tissue and lymphocytes. *Mol Cell Endocrinol* 9:303-310.
- S65. Bagriacik, E.U., and Klein, J.R. 2000. The Thyrotropin (Thyroid-Stimulating Hormone) Receptor Is Expressed on Murine Dendritic Cells and on a Subset of CD45RB<sup>high</sup> Lymph Node T Cells: Functional Role for Thyroid-Stimulating Hormone During Immune Activation. *J Immunol* 164:6158-6165.
- S66. Murakami, M., Hosoi, Y., Negishi, T., Kamiya, Y., Miyashita, K., Yamada, M., Iriuchijima, T., Yokoo, H., Yoshida, I., Tsushima, Y., et al. 1996. Thymic hyperplasia in patients with Graves' disease. Identification of thyrotropin receptors in human thymus. *J Clin Invest* 98:2228-2234.
- S67. Brokken, L.J.S., Scheenart, J.W.C., Wiersinga, W.M., and Prummel, M.F. 2001. Suppression of serum TSH by Graves' Ig: Evidence for a functional pituitary TSH receptor. *J Clin Endocrinol Metab* 86:4814-4817.
- S68. Prummel, M.F., Brokken, L.J.S., Meduri, G., Misrahi, M., Bakker, O., and Wiersinga, W.M. 2000. Expression of the thyroid-stimulating hormone receptor in the folliculo-stellate cells of the human anterior pituitary. *J Clin Endocrinol Metab* 85:4347-4353.
- S69. Davies, T., Smith, B., and Hall, R. 1978. Binding of thyroid stimulators to guinea pig testis and thyroid. *Endocrinology* 103:6-10.
- S70. Kumar, R.S., Ijiri, S., Kight, K., Swanson, P., Dittman, A., Alok, D., Zohar, Y., and Trant, J.M. 2000. Cloning and functional expression of a thyrotropin receptor from the gonads of a vertebrate (bony fish): potential thyroid-independent role for thyrotropin in reproduction. *Mol Cell Endocrinol* 167:1-9.
- S71. Sellitti, D.F., Akamizu, T., Doi, S.Q., Kim, G.H., Kariyil, J.T., Kopchik, J.J., and Koshiyama, H. 2000. Renal expression of two 'thyroid-specific' genes:

thyrotropin receptor and thyroglobulin. *Exp Nephrol* 8:235-243.

S72. Crisanti, P., Omri, B., Hughes, E.J., Meduri, G., Hery, C., Clauser, E., Jacquemin, C., and Saunier, B. 2001. The Expression of Thyrotropin Receptor in the Brain. *Endocrinology* 142:812-822.

S73. Cornelius, P., MacDougald, O.A., and Lane, M.D. 1994. Regulation of adipocyte development. *Annu Rev Nutr* 14:99-129.

S74. Haraguchi, K., Shimura, H., Lin, L., Endo, T., and Onaya, T. 1996. Differentiation of rat preadipocytes is accompanied by expression of thyrotropin receptors. *Endocrinology* 137:3200-3205.

S75. Endo, T., Ohta, K., Haraguchi, K., and Onaya, T. 1995. Cloning and Functional Expression of a Thyrotropin Receptor cDNA from Rat Fat Cells. *J. Biol. Chem.* 270:10833-10837.

S76. Roselli-Rehfuss, L., Robbins, L., and Cone, R. 1992. Thyrotropin receptor messenger ribonucleic acid is expressed in most brown and white adipose tissues in the guinea pig. *Endocrinology* 130:1857-1861.

S77. Valyasevi, R.W., Erickson, D.Z., Harteneck, D.A., Dutton, C.M., Heufelder, A.E., Jyonouchi, S.C., and Bahn, R.S. 1999. Differentiation of Human Orbital Preadipocyte Fibroblasts Induces Expression of Functional Thyrotropin Receptor. *J Clin Endocrinol Metab* 84:2557-2562.

S78. Inoue, M., Tawata, M., Yokomori, N., Endo, T., and Onaya, T. 1998. Expression of thyrotropin receptor on clonal osteoblast-like rat osteosarcoma cells. *Thyroid* 8:1059-1064.