

Name : ROGER
First names : Pierre Philippe

1980 Licence en Sciences Chimiques (MS), Free University of Brussels

1984 Doctorat en Sciences (PhD) Free University of Brussels
Section: Biochemistry

PhD Thesis : Contrôle hormonal de la prolifération et de la différenciation de la cellule thyroïdienne in vitro. (Adviser Prof. Jacques E. Dumont)

Present positions : Senior Research Associate (Maître de Recherches) of the National Fund for Scientific Research (Belgium) (FRS-FNRS). WELBIO/ULB Principal Investigator.

AWARDS

- Jean-Servais Stas Prize (Académie Royale de Belgique (1984)).
- Max-Pierre König Prize (European Thyroid Association (1992)).
- **Harrington-De Visscher Prize (European Thyroid Association (1996)).**
- Godin-Savelkoul Prize (Académie Royale de Médecine de Belgique (period 2001-2003)).
- **Triennial cancerology prize of the Alexandre & Gaston Tytgat Foundation (2008)** (shared with C. Maenhaut)
- Investigator/laureate of the Welbio 2011
- Laureate of Fonds Paul Génicot 2014 (ULB)

SCIENTIFIC ACTIVITY

I pioneered the study of proliferation and differentiation of thyroid cells by defining model systems of primary cultures in chemically defined medium (without serum). Using these systems, I demonstrated and characterized the unique coexistence in these cells of two distinct proliferation modes, activated by TSH (only via cAMP elevation and PKA activation) or by several growth factors (via Ras and MAP kinases). The cAMP pathway simultaneously stimulates proliferation and differentiation expression in thyrocytes, and is involved in goitrogenesis and generation of hyperfunctional adenomas, whereas the growth factor pathways induce dedifferentiation and are involved in thyroid carcinomas. In thyroid primary cultures, the positive cell cycle regulation by cAMP is unique as it targets the assembly and then the activation of complexes formed by preexisting cyclin D3 and cyclin-dependent kinase (CDK) 4, without involving most intermediaries of classical mitogenic signaling cascades.

The present research interests of our group include the cellular and molecular features of cell cycle regulation in this model system and several others (investigation of cyclins, CDKs, their inhibitors, the interactions between these different proteins and their posttranslational modifications). Using two-dimensional electrophoresis to separate the phosphorylated forms of these proteins within their various complexes, we identified the activating phosphorylation of CDK4 as a direct crucial target for cell cycle regulation in various cell systems. Using various molecular, cellular, proteomic and bioinformatic approaches, we are currently (i) exploring the mechanisms of this critical CDK4 regulation that determines the inactivation of the central oncosuppressor protein pRb and the cell cycle decision in normal and cancerous cells; (ii) developing novel tools to predict whether cancer patients will benefit or not of treatments with

the new CDK4 inhibitory drugs that are now approved for treatment of advanced ER+ breast cancers.

ADVISER of 9 PhD theses and 21 master theses.

50 MAIN PUBLICATIONS (of 120 peer reviewed papers, > 5750 citations, H=40)

<http://publicationslist.org/pierre.roger>

ROGER, P.P., HOTIMSKY, A., MOREAU, C., DUMONT, J.E.

Stimulation by thyrotropin, cholera toxin and dibutyryl cyclic AMP of the multiplication of differentiated thyroid cells in vitro.
Mol. Cell. Endocrinol. 26, 165-176 (1982).

ROGER, P.P., SERVAIS, P., DUMONT, J.E.

Stimulation by thyrotropin and cyclic AMP of the proliferation of quiescent canine thyroid cells cultured in a defined medium containing insulin.
FEBS Lett. 157, 323-329 (1983).

ROGER, P.P., DUMONT, J.E.

Factors controlling proliferation and differentiation of canine thyroid cells cultured in reduced serum conditions: effects of thyrotropin, cyclic AMP and growth factors.
Mol. Cell. Endocrinol. 36, 79-93 (1984).

ROGER, P.P., VAN HEUVERSWYN, B., LAMBERT, C., REUSE, S., VASSART, G., DUMONT, J.E.

Antagonistic effects of thyrotropin and epidermal growth factor on thyroglobulin mRNA level in cultured thyroid cells.
Eur. J. Biochem. 152, 239-245 (1985).

ROGER, P.P., REUSE, S., SERVAIS, P., VAN HEUVERSWYN, B., DUMONT, J.E.

Stimulation of cell proliferation and inhibition of differentiation expression by tumor-promoting phorbol esters in dog thyroid cells in primary culture.
Cancer Res. 46, 898-906 (1986).

ROGER, P.P., SERVAIS, P., DUMONT, J.E.

Induction of DNA synthesis in dog thyrocytes in primary culture: synergistic effects of thyrotropin and cyclic AMP with epidermal growth factor and insulin.
J. Cell. Physiol. 130, 58-67 (1987).

ROGER, P.P., SERVAIS, P., DUMONT, J.E.

Regulation of dog thyroid epithelial cell cycle by forskolin, an adenylate cyclase activator.
Exp. Cell Res. 172, 282-292 (1987).

DUMONT, J.E., ROGER, P.P., LUDGATE, M.

Assays for thyroid growth immunoglobulins and their clinical applications : methods, concepts and misconceptions.
Endocrine Rev. 8, 448-452 (1987).

ROGER, P.P., TATON, M., VAN SANDE, J., DUMONT, J.E.

Mitogenic effects of thyrotropin and cyclic AMP in differentiated human thyroid cells in vitro.
J. Clin. Endocrinol. Metab. 66, 1158-1165 (1988).

- DUMONT, J.E., JAUNIAUX, J.C., ROGER, P.P.
The cyclic AMP-mediated stimulation of cell proliferation.
Trends Biochem. Sci. 14, 67-71, (1989).
- ROGER, P.P., RICKAERT, F., LAMY, F., AUTHELET, M., DUMONT, J.E.
Actin stress fiber disruption and tropomyosin isoform switching in normal thyroid epithelial cells stimulated by thyrotropin and phorbol esters.
Exp. Cell. Res. 182, 1-13 (1989).
- POHL, V., ROGER, P.P., CHRISTOPHE, D., PATTYN, G., VASSART, G., DUMONT, J.E.
Differentiation expression during proliferative activity induced through different pathways: in situ hybridization study of thyroglobulin gene expression in thyroid epithelial cells.
J. Cell Biol. 111, 663-672 (1990).
- LAMY, F., TATON, M., DUMONT, J.E., ROGER, P.P.
Control of protein synthesis by thyrotropin and epidermal growth factor in human thyrocytes : role of morphological changes.
Mol. Cell. Endocrinol. 73, 195-209 (1990).
- COCLET, J., LAMY, F., RICKAERT, F., DUMONT, J.E., ROGER, P.P.
Intermediate filaments in normal thyrocytes : modulation of vimentin expression in primary cultures.
Mol. Cell Endocrinol. 76, 135-148 (1991).
- DUMONT, J.E., MAENHAUT, C., PIRSON, I., BAPTIST, M., ROGER, P.P.
Growth factors controlling the thyroid gland.
Baillière's Clinical Endocrinol. Metab. 5, 727-754 (1991).
- ROGER, P.P., BAPTIST, M., DUMONT, J.E.
A mechanism generating heterogeneity in thyroid epithelial cells : suppression of the thyrotropin/cAMP-dependent mitogenic pathway after cell division induced by cAMP-independent factors.
J. Cell Biol. 117, 383-393 (1992).
- DUMONT, J.E., LAMY, F., ROGER, P., MAENHAUT, C.
Physiological and pathological regulation of thyroid cell proliferation and differentiation by thyrotropin and other factors: an example of positive control of proliferation and differentiation by the cyclic AMP cascade.
Physiol. Rev. 72, 667-697 (1992).
- BAPTIST, M., DUMONT, J.E., ROGER, P.P.
Demonstration of cell cycle kinetics in thyroid primary culture by immunostaining of proliferating cell nuclear antigen : differences in cyclic AMP-dependent and independent mitogenic stimulations.
J. Cell. Sci. 105, 69-80 (1993).
- ROGER, P.P., REUSE, S., MAENHAUT, C., DUMONT, J.E.
Multiple facets of the modulation of growth by cyclic AMP
Vitamins and Hormones, 51, 59-191 (1995).
- BAPTIST, M., DUMONT, J.E., ROGER, P.P.
Intercellular heterogeneity of early mitogenic events: cAMP generalizes the EGF effect on c-Fos protein appearance but not on MAP kinase phosphorylation and nuclear translocation in dog thyroid epithelial cells.
Exp. Cell Res. 221, 160-171 (1995).

- BAPTIST, M., LAMY, F., GANNON, J., HUNT, T., DUMONT, J.E., ROGER, P.P.
Expression and subcellular localization of CDK2 and cdc2 kinases and their common partner cyclin A in thyroid epithelial cells: comparison of cyclic AMP-dependent and -independent cell cycles.
J. Cell. Physiol. 166, 256-273 (1996).
- DEPOORTERE, F., DUMONT, J.E., ROGER, P.P.
Paradoxical accumulation of the cyclin-dependent kinase inhibitor p27^{KIP1} during the cAMP-dependent mitogenic stimulation of thyroid epithelial cells.
J. Cell Sci., 109, 1759-1764 (1996).
- BURIKHANOV, R., COULONVAL, K., PIRSON, I., LAMY, F., DUMONT, J.E., ROGER, P.P.
Thyrotropin via cyclic AMP induces insulin receptor expression and insulin co-stimulation of growth and amplifies insulin and insulin-like growth factor signalling pathways in dog thyroid epithelial cells.
J. Biol. Chem. 271, 29400-29406 (1996).
- ROGER, P.P., CHRISTOPHE, D., DUMONT, J.E., PIRSON, I.
The dog thyroid primary culture system: a model of the regulation of function, growth and differentiation by cyclic AMP and other well defined signaling cascades (invited review).
Eur. J. Endocrinol. 137, 579-598 (1997).
- DEPOORTERE, F., VAN KEYMEULEN, A., LUKAS, J., COSTAGLIOLA, S., BARTKOVA, J., DUMONT, J.E., BARTEK, J., ROGER, P.P. (corresponding author), DREMIER, S.
A requirement for cyclin D3-cyclin-dependent kinase (cdk)-4 assembly in the cyclic adenosine monophosphate-dependent proliferation of thyrocytes.
J. Cell Biol. 140, 1427-1439 (1998).
- ROGER, P.P., DEMARTIN, S., DUMONT, J.E.
Nature of the critical labile event that controls RB phosphorylation in the cyclic AMP-dependent cell cycle of thyrocytes in primary culture.
Exp. Cell Res. 252, 492-498 (1999).
- VAN KEYMEULEN, A., BARTEK, J., DUMONT, J.E., ROGER, P.P.
Cyclin D3 accumulation and activity integrate and rank the comitogenic pathways of thyrotropin and insulin in thyrocytes in primary culture.
Oncogene 18, 7351-7359 (1999).
- DEPOORTERE, F., PIRSON, I., BARTEK, J., DUMONT, P.P., ROGER, P.P.
Transforming growth factor β 1 selectively inhibits the cyclic AMP-dependent proliferation of primary thyroid epithelial cells by preventing the association of cyclin D3-cdk4 with nuclear p27^{KIP1}.
Mol. Biol. Cell 11, 1061-1076 (2000).
- VAN KEYMEULEN, A., DELEU, S., BARTEK, J., DUMONT, J.E., ROGER, P.P.
Respective roles of carbamylcholine and cyclic adenosine monophosphate in their synergistic regulation of cell cycle in thyroid primary cultures.
Endocrinology 142, 1251-1259 (2001).
- KIMURA, T., VAN KEYMEULEN, A., GOLSTEIN, J., FUSCO, A., DUMONT, J.E., ROGER, P.P.
Regulation of thyroid cell proliferation by TSH and other factors : a critical evaluation of in vitro models.
Endocrine Rev. 22, 631-656 (2001).

- PATERNOT, S., COULONVAL, K., DUMONT, J.E., ROGER, P.P.
Cyclic AMP-dependent phosphorylation of cyclin D3-bound CDK4 determines the passage through the cell cycle restriction point in thyroid epithelial cells.
J. Biol. Chem. 278, 26533-26540 (2003).
- COULONVAL, K., BOCKSTAELE, L., PATERNOT, S., DUMONT, J.E., ROGER, P.P.
The cyclin D3-CDK4-p27^{kip1} holoenzyme in thyroid epithelial cells : activation by TSH, inhibition by TGF β , and phosphorylations of its subunits demonstrated by two-dimensional gel electrophoresis.
Exp. Cell Res. 291, 135-149 (2003).
- COULONVAL, K., BOCKSTAELE, L., PATERNOT, S., ROGER, P.P.
Phosphorylations of cyclin-dependent kinase 2 revisited using two-dimensional gel electrophoresis.
J. Biol. Chem. 278, 52052-52060 (2003).
- ARSENIJEVIC, T., DEGRAEF, C., DUMONT, J.E., ROGER, P.P., PIRSON, I.
A novel partner for cyclins D: Protein Kinase A-anchoring protein AKAP95.
Biochem. J. 378, 673-679 (2004).
- FORTEMAISON, F., BLANCQUAERT, S., DUMONT, J.E., MAENHAUT, C., AKTORIES, K., ROGER, P.P.(corresponding author), DREMIER, S.
Differential involvement of the actin cytoskeleton in differentiation and mitogenesis of thyroid cells : Inactivation of Rho proteins contributes to cAMP-dependent gene expression but prevents mitogenesis.
Endocrinology 146, 5845-5495 (2005).
- PATERNOT, S., ARSENIJEVIC, T., COULONVAL, K., BOCKSTAELE, L., DUMONT, J.E., ROGER, P.P.
Distinct specificities of pRb phosphorylation by CDK4 activated by cyclin D1 or cyclin D3: differential involvement in the distinct mitogenic modes of thyroid epithelial cells.
Cell Cycle 5, 61-70 (2006).
- BOCKSTAELE, L., KOOKEN, H., LIBERT, F., PATERNOT, S., DUMONT, J.E., de LAUNOIT, Y., ROGER, P.P.(corresponding author), COULONVAL, K.
Thr172-phosphorylation of CDK4: its relationship with cyclins and CDK "inhibitors".
Mol. Cell Biol. 26, 5070-5085 (2006).
- PATERNOT, S., DUMONT, J.E., ROGER, P.P.
Differential utilization of cyclin D1 and cyclin D3 in the distinct mitogenic stimulations by growth factors and TSH of human thyrocytes in primary culture.
Mol. Endocrinol. 20, 3279-3292 (2006).
- BOCKSTAELE, L., COULONVAL, K., KOOKEN, H., PATERNOT, S., ROGER, P.P.
Regulation of CDK4 (invited review).
Cell Div. (BioMed Central) 1, n° 25 (2006).
<http://www.celldiv.com/content/1/1/25>.
- DREMIER, S., MILENKOVIC, M., BLANCQUAERT, S., DUMONT, J.E., DOSKELAND, S.O., MAENHAUT, C., ROGER, P.P.
Cyclic adenosine 3',5'-monophosphate (cAMP)-dependent protein kinases, but not exchange proteins directly activated by cAMP (Epac), mediate thyrotropin/cAMP-dependent regulation of thyroid cells.
Endocrinology, 148, 4612-4622 (2007).

ROCHA, A.S., PATERNOT, S., COULONVAL, K., DUMONT, J.E., SOARES, P., ROGER P.P.
Cyclic AMP inhibits the proliferation of thyroid carcinoma cell lines through regulation of CDK4 phosphorylation.
Mol. Biol. Cell, 19, 4814-4825 (2008).

PATERNOT, S., ROGER, P.P.
Combined inhibition of MEK and mammalian target of rapamycin abolishes phosphorylation of cyclin-dependent kinase 4 in glioblastoma cell lines and prevents their proliferation.
Cancer Res. 69, 4577-4581 (2009).

BOCKSTAELE, L.*, BISTEAU, X.* (*equal contribution), PATERNOT, S., ROGER, P.P.
Differential regulation of CDK4 and CDK6, evidence that CDK4 might not be activated by CDK7, and design of a CDK6 activating mutation.
Mol. Cell. Biol., 29,4188-4200 (2009).

PATERNOT, S., BOCKSTAELE, L., BISTEAU, X., KOOKEN, H., COULONVAL, K., ROGER, P.P.
Rb inactivation in cell cycle and cancer : The puzzle of highly regulated activating phosphorylation of CDK4 versus constitutively active CDK-activating kinase (invited perspective).
Cell Cycle 9, 689-699 (2010).

BLANCQUAERT, S, WANG, L, PATERNOT, S, COULONVAL, K, DUMONT, JE, HARRIS, TE, ROGER, PP.
Cyclic AMP-dependent activation of mammalian target of rapamycin (mTOR) in thyroid cells. Implication in mitogenesis and activation of CDK4.
Mol. Endocrinol. 24, 1453-1468 (2010).

COULONVAL, K., KOOKEN, H., ROGER, P.P.
Coupling of T161 and T14 phosphorylations protects cyclin B-CDK1 from premature activation.
Mol. Biol. Cell, 22, 3971-3985 (2011).

BISTEAU, X.*, PATERNOT, S.* (*equal contribution), COLLEONI, B., COULONVAL, K., ECKER, K., DE GROOTE, P., DECLERCQ, W., HENGST, L., ROGER, P.P.
CDK4 T172-phosphorylation is central in a CDK7-dependent bidirectional CDK4/CDK2 interplay mediated by p21 phosphorylation at the restriction point.
PLoS Genetics, 9(5) e1003546 (2013)(21 pages ; 11 suppl. figures).

PATERNOT, S., COLLEONI, B., BISTEAU, X., ROGER, P.P.
The CDK4/CDK6 inhibitor PD0332991 paradoxically stabilizes activated cyclin D3-CDK4/6 complexes.
Cell Cycle, 13, 2879-2888 (2014).

BIANCA COLLEONI*, SABINE PATERNOT* (equal contributions), JAIME M PITA, XAVIER BISTEAU, KATIA COULONVAL, ROGER J DAVIS, ERIC RASPÉ, PIERRE P. ROGER.
JNKs function as CDK4-activating kinases by phosphorylating CDK4 and p21.
Oncogene, 2017 Apr 3. doi: 10.1038/onc.2017.7. [Epub ahead of print]

ERIC RASPÉ, KATIA COULONVAL*, JAIME M. PITA*, SABINE PATERNOT*, FRANÇOISE ROTHÉ* (essential contributions), LAURE TWYFFELS, SYLVAIN BROHÉE, LIGIA CRACIUN, DENIS LARSIMONT, VÉRONIQUE KRUYIS, FLAVIENNE SANDRAS, ISABELLE SALMON, STEVEN VAN LAERE, MARTINE PICCART, MICHAÏL IGNATIADIS, CHRISTOS SOTIRIOU, PIERRE P. ROGER.
CDK4 phosphorylation status and corresponding gene expression profile predict sensitivity to Palbociclib.
EMBO Mol. Med. Accepted May, 2017.