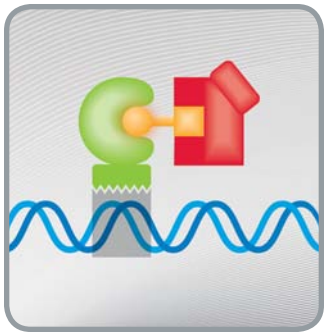
Inducible Gene Expression Citations

The ARGENT Regulated Transcription Plasmid Kit and AP21967 (previously available from ARIAD Pharmaceuticals, Inc.) are now available from Clontech as the **iDimerize™ Inducible Expression System** and A/C Heterodimerizer. The Inducible Expression System can be used to control transcription activation of target genes.



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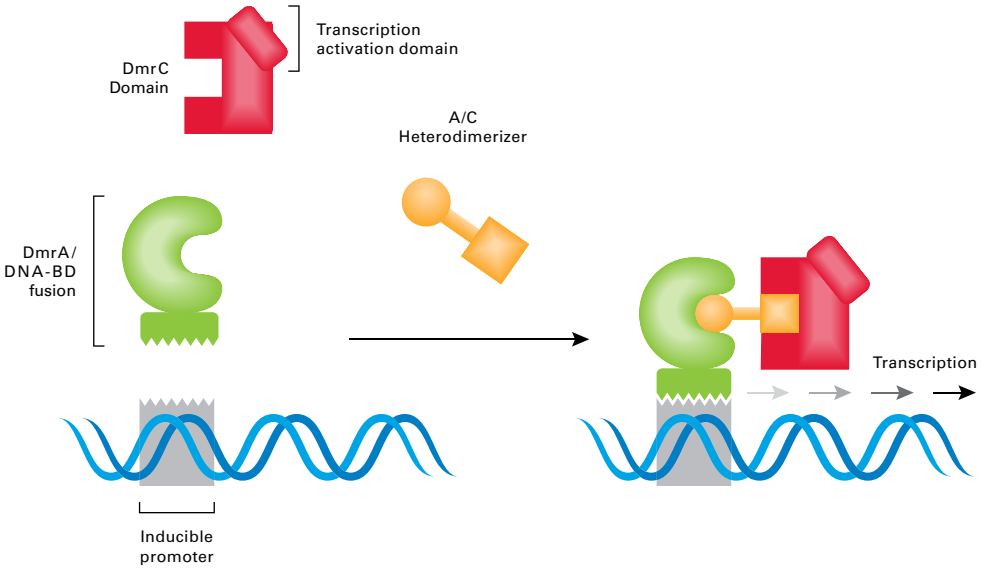

Transcription factors are bifunctional proteins that recognize specific DNA sequences near target genes (via the DNA binding domain) and then recruit the transcriptional machinery of the cell to activate transcription (via the transcription activation domain.) These two domains can work together to activate transcription even when they are expressed as individual proteins and brought together by the A/C Heterodimerizer ligand.

Products

ARIAD/ARGENT Product	Clontech Product	Cat. #	Package Size
ARGENT Regulated Transcription Plasmid Kit	iDimerize Inducible Expression System	635065	each
AP21967	A/C Heterodimerizer	635057 635056 635055	500 µl 5 x 500 µl 5 mg

Each system contains a vector set and 500 µl (0.5 mM) ligand.

Notice to Purchaser

Your use of these products and technologies is subject to compliance with any applicable licensing requirements described on the product's web page at http://www.clontech.com. It is your responsibility to review, understand and adhere to any restrictions imposed by such statements.

2011 Citations

Hagan, C. R. *et al.* (2011) *Mol. Cell Biol.* **31**(12):2439–2452. Ck2-dependent phosphorylation of progesterone receptors (PR) on Ser81 regulates PR-B isoform-specific target gene expression in breast cancer cells. Progesterone Receptor B was inducibly expressed in breast cancer cells in the absence of exogenously added progestins, to demonstrate that some PR-B regulated genes are regulated ligand-independently.

2010 Citations

Grünberg, R. *et al.* (2010) *Nucleic Acids Res.* **38**(8):2645–2662. Building blocks for protein interaction devices. FRET and the ARGENT system were combined, to demonstrate the feasibility of parts-based protein synthetic biology and modular design.

Varma, D. *et al.* (2010) *Proc. Natl. Acad. Sci. USA* **107**(8):3493–3498. Development and application of in vivo molecular traps reveals that dynein light chain occupancy differentially affects dynein-mediated processes. Demonstrated the specificity and efficacy of chemically induced dimeric "traps" for the dynein light chains LC8 (DynII1) and TcTex1 (DynIt1).

2008 Citations

Vogel, R., Mammeri, H., and Mallet, J. (2008) *Hum. Gene Ther.* **19**(2):167–178. Lentiviral vectors mediate nonimmunosuppressive rapamycin analog-induced production of secreted therapeutic factors in the brain: regulation at the level of transcription and exocytosis. AP21967 was used to control expression and secretion of glial cell line-derived neurotrophic factor (GDNF) in the striata of mice.

2007 Citations

Fang, J. *et al.* (2007) *Mol. Ther.* **15**(6):1153–1159. An antibody delivery system for regulated expression of therapeutic levels of monoclonal antibodies *in vivo*. A rapamycin-controlled system for inducible high-level expression of unmodified mAbs *in vivo*.

Nguyen, M. *et al.* (2007) *Mol. Ther.* **15**(5):912–920. Rapamycin-regulated control of antiangiogenic tumor therapy following rAAV-mediated gene transfer. Dimerizer-regulated VEGF gene expression significantly decreased tumor growth in two subcutaneous models of glioblastoma.

Ostrander, J. H. *et al.* (2007) *Cancer Res.* **67**(9):4199–4209. Breast tumor kinase (protein tyrosine kinase 6) regulates heregulin-induced activation of ERK5 and p38 MAP kinases in breast cancer cells. MCF-10A cells stably expressing inducible Brk proteins were treated with AP21967 to induce Brk expression and activate downstream pathways essential to breast cancer cell migration.

Varma, H., Skildum, A. J., and Conrad, S. E. (2007) *PLoS ONE* **2**(12):e1256. Functional ablation of pRb activates Cdk2 and causes antiestrogen resistance in human breast cancer cells. The ARGENT gene expression system was used to test the roles of Cdk2 and Cdk4 in the inactivation of retinoblastoma protein (pRb) family tumor suppressors.

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Indraccolo, S. *et al.* (2006) *Gene Ther.* **13**(12):953–965. Gene therapy of ovarian cancer with IFN-alpha-producing fibroblasts: comparison of constitutive and inducible vectors. AP21967 and the retroviral ARGENT gene expression system were used to control interferon-alpha expression in mice.

Koh, J. T. *et al.* (2006) *Mol. Ther.* **14**(5):684–691. Use of a stringent dimerizer-regulated gene expression system for controlled BMP2 delivery. AP21967-controlled expression of BMP2 was used to induce bone formation *in vitro.*

Leitner, N. R. *et al.* (2006) *BMC Biotechnol.* **6**:48. A time- and dose-dependent STAT1 expression system. Dimerizer was used to control STAT1 function in a time- and dose-dependent manner *in vivo* and in transgenic mice.

Pike, L., Petravicz, J., and Wang, S. (2006) *J. Gene Med.* **8**(7):804–813. Bioluminescence imaging after HSV amplicon vector delivery into brain. Dose-dependent expression of firefly luciferase was used for fast, non-invasive, semi-quantitative analysis of gene expression in the brain.

Sanftner, L. M. *et al.* (2006) *Mol. Ther.* **13**(1):167–174. Dimerizer regulation of AADC expression and behavioral response in AAV-transduced 6-OHDA lesioned rats. Rapamycin-regulated control of AADC in the striata was used to study behavioral effects in a rat model of Parkinson's disease.

Schachter, K. A. *et al.* (2006) *J. Biol. Chem.* **281**(28):19134–19144. Dynamic positive feedback phosphorylation of mixed lineage kinase 3 by JNK reversibly regulates its distribution to Triton-soluble domains. AP21967 was used to study MLK regulation by JNK in the MCF-7 human breast cancer cell line.

Valenta, T. *et al.* (2006) *EMBO J.* **25**(11):2326–2337. HIC1 attenuates Wnt signaling by recruitment of TCF-4 and beta-catenin to the nuclear bodies. The zinc-finger transcription factor hypermethylated in cancer 1 (HIC1) was used to modulate genes regulated by canonical Wnt/beta-catenin signaling.

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2005 Citations

Lebherz, C. *et al.* (2005) *Hum. Gene Ther.* **16**(2):178–186. Long-term inducible gene expression in the eye via adeno-associated virus gene transfer in nonhuman primates. Rapamycin and AP22594 were used for long-term regulation of erythropoietin expression in the eyes of nonhuman primates.

Mukherjee, S., and Conrad, S. E. (2005) *J. Biol. Chem.* **280**(18):17617–17625. c-Myc suppresses p21WAF1/CIP1 expression during estrogen signaling and antiestrogen resistance in human breast cancer cells. The AP1510 homodimerization system was used to regulate transcription of c-Myc in stably transduced MCF-7 cells.

Rivera, V. M. *et al.* (2005) *Blood* **105**(4):1424–1430. Long-term pharmacologically regulated expression of erythropoietin in primates following AAV-mediated gene transfer. Long-term (> 6 years) rapamycin- and AP22594-regulated expression of erythropoietin in nonhuman primates.

2004 Citations

Horswill, A. R., Savinov, S. N., and Benkovic, S. J. (2004) *Proc. Natl. Acad. Sci. USA* **101**(44):15591–15596. A systematic method for identifying small-molecule modulators of protein-protein interactions. Rapamycin was used to control transcription in *E. coli* and to identify inhibitors of protein-protein interactions.

Sudomoina, M. *et al.* (2004) *BMC Biotechnol.* **4**:9. A gene expression system offering multiple levels of regulation: the Dual Drug Control (DDC) system. AP21967-mediated transcription of a tetracycline-regulated transcription factor was used to control target gene expression.

Wang, J. *et al.* (2004) *Gene Ther.* **11**(8):729–733. Rapamycin control of exocrine protein levels in saliva after adenoviral vector-mediated gene transfer. The first demonstration of rapamycin-regulated gene expression in rat salivary glands.

Zhang, H. *et al.* (2004) *J. Biol. Chem.* **279**(19):19457–19463. Hsp90/p50cdc37 is required for mixed-lineage kinase (MLK) 3 signaling. AP21967 was used to induce the expression of mixed-lineage kinase 3 in stable cell lines to study its function.

2003 Citations

Crittenden, M., *et al.* (2003) *Cancer Res.* **63**(12):3173–3180. Pharmacologically regulated production of targeted retrovirus from T cells for systemic antitumor gene therapy. T cells were modified to produce a retrovirus under tight pharmacological control, using AP21967. Systemic delivery of tumor-specific T cells to mice bearing metastatic tumors caused recruitment of nonspecific T cells to the tumor site.

Johnston, J. *et al.* (2003) *Mol. Ther.* **7**(4):493–497. Regulated expression of erythropoietin from an AAV vector safely improves the anemia of beta-thalassemia in a mouse model. Rapamycin-mediated control of Epo was used to treat anemia in beta-thalassemic mice. The Epo levels and hematocrit were rapamycin-dependent.

Wang, S., Petravicz, J., and Breakefield, X. O. (2003) *Mol. Ther.* **7**(6):790–800. Single HSV-amplicon vector mediates drug-induced gene expression via dimerizer system. Rapamycin-dependent expression of a reporter gene was studied in culture (primary cell and organotypic cultures) and in rat brain.

Xu, Z. L. *et al.* (2003) *Gene* **309**(2):145–151. Regulated gene expression from adenovirus vectors: a systematic comparison of various inducible systems. In a direct comparison of five different gene regulation systems, the AP21967-based dimerizer system had the lowest basal expression and highest induction ratio.

Yang, W. *et al.* (2003) *Bioorg. Med. Chem. Lett.* **13**(19):3181–3184. Regulation of gene expression by synthetic dimerizers with novel specificity. A structure-activity study of synthetic homodimerizers, for gene transcription regulation.

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Auricchio, A. *et al.* (2002) *Gene Ther.* **9**(14):963–971. Constitutive and regulated expression of processed insulin following *in vivo* hepatic gene transfer. Demonstrated tight, rapamycin-dependent transcription of insulin and control of glucose levels in the mouse liver.

Auricchio, A. *et al.* (2002) *Mol. Ther.* **6**(2):238–242. Pharmacological regulation of protein expression from adeno-associated viral vectors in the eye. Demonstrated tight, dose-dependent regulation of gene expression in the eyes of rats and primates, following systemic administration of rapamycin.

Chong, H. *et al.* (2002) *Mol. Ther.* **5**(2):195–203. A system for small-molecule control of conditionally replication-competent adenoviral vectors. The rapamycin analog AP21967 was used to control E1 gene expression and adenoviral vector replication *in vitro* and *in vivo.*

Go, W. Y., and Ho, S. N. (2002) *J. Gene Med.* **4**(3):258–270. Optimization and direct comparison of the dimerizer and reverse tet transcriptional control systems. Demonstrated tight, rapamycin-induced gene expression in transiently transfected cells.

Pollock, R., and Clackson, T. (2002) *Curr. Opin. Biotechnol.* **13**(5):459–467. Dimerizer-regulated gene expression. A review of dimerizer-based systems for regulating gene expression.

Pollock, R. *et al.* (2002) *Nat. Biotechnol.* **20**(7):729–733. Regulation of endogenous gene expression with a small-molecule dimerizer. Dimerizer-regulated gene expression was combined with targeted zinc finger DNA binding domain technology to permit small molecule control of endogenous gene expression. AP21967-dependent expression of the chromosomal human VEGF gene was rapid, tight, and dose-dependent—and exceeded levels produced by the natural hypoxic response.

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Senner, V., Sotoodeh, A., and Paulus, W. (2001) *Neurochem. Res.* **26**(5):521–524. Regulated gene expression in glioma cells: a comparison of three inducible systems. The AP1510-based transcriptional regulation system was used to achieve tight, highly-inducible gene expression in glioma cells.

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Clackson, T. (2000) *Gene Ther.* **7**(2):120–125. Regulated gene expression systems. A review of systems for regulating gene expression (for gene therapy).

Pollock, R. *et al.* (2000) *Proc. Natl. Acad. Sci. USA* **97**(24):13221–13226. Delivery of a stringent dimerizer-regulated gene expression system in a single retroviral vector. Rapamycin- or rapalog-regulated transcription in a variety of cell lines gave negligible basal expression and induction ratios of at least three orders of magnitude.

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Molinari, E., Gilman, M., and Natesan, S. (1999) *EMBO J.* **18**(22):6439–6447. Proteasome-mediated degradation of transcriptional activators correlates with activation domain potency *in vivo*. Rapamycin-regulated recruitment of a transcription activation domain was used to explore proteasome-mediated degradation of transcription factors.

Natesan, S. *et al.* (1999) *Proc. Natl. Acad. Sci. USA* **96**(24):13898–13903. A general strategy to enhance the potency of chimeric transcriptional activators. The effectiveness of chimeric transcriptional activators was dramatically improved by expressing them as noncovalent tetrameric bundles.

Pollock, R., and Rivera, V. M. (1999) *Methods Enzymol.* **306**:263–281. Regulation of gene expression with synthetic dimerizers. Describes the development of a transcription switch based on the synthetic homodimerizer, AP1889, which binds specifically to a mutated FKBP.

Rivera, V. M. *et al.* (1999) *Proc. Natl. Acad. Sci. USA* **96**(15):8657–8662. Long-term regulated expression of growth hormone in mice after intramuscular gene transfer. A rapamycin-regulated transcription system for long-term, tightly regulated control over the production of growth hormone in mice.

Ye, X. *et al.* (1999) *Science* **283**(5398):88–91. Regulated delivery of therapeutic proteins after *in vivo* somatic cell gene transfer. The first demonstration of regulated gene expression in a primate. Rapamycin regulated transcription was used to control erythropoietin expression in mice and a non-human primate.

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Rivera, V. M. (1998) *Methods* **14**(4):421–429. Controlling gene expression using synthetic ligands. A detailed description of the AP1510-based dimerizer system for transcription control.

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Amara, J. F. *et al.* (1997) *Proc. Natl. Acad. Sci. USA* **94**(20):10618–10623. A versatile synthetic dimerizer for the regulation of protein-protein interactions. AP1510-mediated oligomerization of a Fas receptor and an engineered transcription factor induced apoptosis and target gene transcription, respectively.

Clackson, T. (1997) *Curr. Opin. Chem. Biol.* **1**(2):210–218. Controlling mammalian gene expression with small molecules. A review of regulatory systems for controlling gene transcription, including the rapamycin-based system.

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Liberles, S. D. *et al.* (1997) *Proc. Natl. Acad. Sci. USA* **94**(15):7825–7830. Inducible gene expression and protein translocation using nontoxic ligands identified by a mammalian three-hybrid screen. The rapamycin heterodimerizer system was modified to function with non-immunosuppressive analogs and used to control the subcellular localization of a protein and the activity of a transcription factor.

Magari, S. R. *et al.* (1997) *J. Clin. Invest.* **100**(11):2865–2872. Pharmacologic control of a humanized gene therapy system implanted into nude mice. Demonstrated precise control of human growth hormone expression in response to rapamycin.

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Belshaw, P. J. *et al.* (1996) *Proc. Natl. Acad. Sci. USA* **93**(10):4604–4607. Controlling protein association and subcellular localization with a synthetic ligand that induces heterodimerization of proteins. An FKBP-cyclophilin heterodimerizer (FKCsA) was used to alter the subcellular localization of a fusion protein and control transcription factor activity.

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