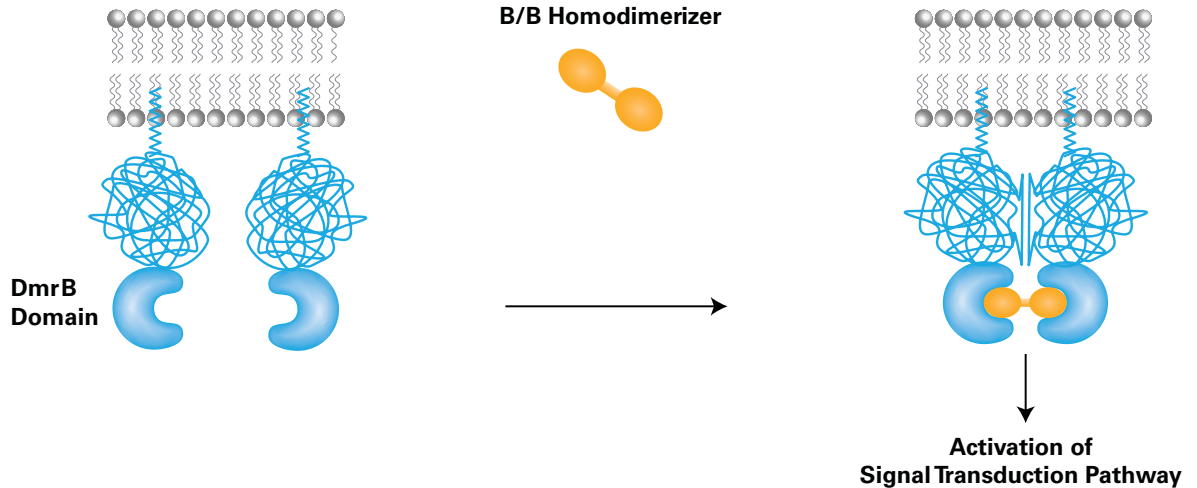


# Inducible Homodimerization Citations

Clontech's **iDimerize™ Inducible Homodimer System** was previously available from ARIAD as the ARGENT Regulated Homodimerization Kit and AP20187 ligand.

## Homodimerization



Fusion proteins containing the DmrB domain do not interact until the B/B Homodimerizer is added. This cell-permeable ligand induces the fusion proteins to interact, activating downstream signaling in real time. This example shows activation of a signal transduction pathway through dimerization of a membrane-bound receptor domain.

## 2011

Choi, R. Y., *et al.* (2011) *Invest. Ophthalmol. Vis. Sci.* **52**(1):364–373. [Cone degeneration following rod ablation in a reversible model of retinal degeneration.](#) Transgenic *X. laevis* expressing the *Escherichia coli* enzyme nitroreductase (NTR) under the control of the rod-specific rhodopsin (XOP) promoter were used to determine the effects of metronidazole on the vision and retinas of XOPNTR F1 tadpoles.

Chow, A., *et al.* (2011) *J. Exp. Med.* **208**(2):261–271. [Bone marrow CD169+ macrophages promote the retention of hematopoietic stem and progenitor cells in the mesenchymal stem cell niche.](#) AP20187-treated MaFIA mice were used to study HSC/progenitor maintenance during homeostasis.

Itakura, E. and Mizushima, N. (2011) *J. Cell Biol.* **192**(1):17–27. [p62 Targeting to the autophagosome formation site requires self-oligomerization but not LC3 binding.](#) Self-oligomerization of p62 is essential for its localization to the autophagosome formation site.

ARIAD/ARGENT Product	Clontech Product	Size	Cat. No.
ARGENT Regulated Homodimerization Kit	iDimerize Inducible Homodimer System	each	635068
AP20187	B/B Homodimerizer	500 µl 5 x 500 µl 5 mg	635060 635059 635058

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

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# Inducible Homodimerization Citations

## 2011 continued

Lange, C. *et al.* (2011) *Mol. Biol. Evol.* **28**(5):1687–1702. [Defining the Origins of the NOD-Like Receptor System at the Base of Animal Evolution](#). The authors show induced proximity recruitment of an effector caspase (HyDD-Caspase) to the HyNLR type 1 protein upon oligomerization, indicating a potential role of caspase activation downstream of NLR activation in Hydra.

Ngo, M. C. *et al.* (2011) *Hum. Mol. Genet.* [Epub ahead of print] [Ex vivo gene transfer for improved adoptive immunotherapy of cancer](#). Adoptive lymphocytes have been genetically modified to improve activity and circumvent tumor evasion, via transfer of transgenic T-cell receptors and chimeric antigen receptors to redirect T cell and natural killer cell antigen specificity, and suicide gene 'safety switches.'

Okazuka, K. *et al.* (2011) *Mol. Ther.* [Epub ahead of print] [Long-term Regulation of Genetically Modified Primary Hematopoietic Cells in Dogs](#). Nine years ago, two dogs were transplanted with autologous marrow CD34(+) cells encoding a conditionally activatable derivative of the thrombopoietin receptor. Receptor activation through administration of a chemical inducer of dimerization (CID) (AP20187 or AP1903) conferred a growth advantage.

Sakai, T. *et al.* (2011) *Proc. Natl. Acad. Sci. USA* **108**(17):7028–7033. [Cargo binding activates myosin VIIA motor function in cells](#). The forced dimer of myosin VIIA translocated its cargo molecule, MyRip, to the tip of filopodia, whereas myosin VIIA without the forced dimer-forming module does not translocate to the filopodial tips.

Soderquest, K. *et al.* (2011) *Blood* **117**(17):4511–4518. [Monocytes control natural killer cell differentiation to effector phenotypes](#). *In vivo* depletion of myeloid cells demonstrates that spleen monocytes mediate the terminal differentiation of peripheral NK cells.

Sun, K., Gan, Y., and Metzger, D. W. (2011) *Infect. Immun.* [Epub ahead of print] [Analysis of murine genetic predisposition to pneumococcal infection reveals a critical role of alveolar macrophages in maintaining the sterility of the lower respiratory tract](#). Administration of the dimerizing reagent, AP20187, induces apoptosis in macrophages and dendritic cells of B6 and 129Sv mice.

Zlatic, S. A. *et al.* (2011) *Mol. Biol. Cell* [Epub ahead of print] [Clathrin-Dependent Mechanisms Modulate the Subcellular Distribution of Class C Vps/HOPS Tether Subunits in Polarized and Non-Polarized Cells](#). Vps class C/HOPS subunits were concentrated at tips of neuronal processes and their delivery was impaired by expression of FKBP-clathrin chimeras and AP20187 incubation.

## 2010

Chen, J. *et al.* (2010) *Proc. Natl. Acad. Sci. USA* **107**(39):16846–16851. [Design of embedded chimeric peptide nucleic acids that efficiently enter and accurately reactivate gene expression in vivo](#). A chimeric peptide nucleic acid (PNA) reactivates the human fetal gamma-globin transcript in adult transgenic mouse bone marrow and human primary peripheral blood cells.

Dixon, J. E. *et al.* (2010) *Development* **137**(18):2973–2980. [Axolotl Nanog activity in mouse embryonic stem cells demonstrates that ground state pluripotency is conserved from urodele amphibians to mammals](#). AxNanog dimers are required to rescue LIF-independent self-renewal and promote proliferation.

Hofman, E. G. *et al.* (2010) *J. Biol. Chem.* **285**(50):39481–39489. [Ligand-induced EGF receptor oligomerization is kinase-dependent and enhances internalization](#). EGF receptor (EGFR) oligomerization was controlled using AP20187 to enhance EGF-induced receptor internalization, and monitored using FRET.

# Inducible Homodimerization Citations

## 2010 continued

Jiang, Z. *et al.* (2010) *J. Neurosci.* **30**(7):2582–2594. [eIF2 \$\alpha\$  Phosphorylation-dependent translation in CA1 pyramidal cells impairs hippocampal memory consolidation without affecting general translation.](#) Conditional transgenic mice were treated with AP20187 to increase PKR-mediated phosphorylation of eIF2 alpha in hippocampal CA1 pyramidal cells, which led to impaired hippocampal late phase-LTP and memory consolidation, but no obvious reduction in general translation.

Karulf, M. *et al.* (2010) *J. Immunol.* **185**(8):4856–4862. [OX40 ligand regulates inflammation and mortality in the innate immune response to sepsis.](#) MaFIA mice were used to determine the role of OX40-OX40 ligand (OX40L) interaction in the innate immune response to polymicrobial sepsis.

Krishnamurthy, S. *et al.* (2010) *Cancer Res.* **70**(23):9969–9978. [Endothelial cell-initiated signaling promotes the survival and self-renewal of cancer stem cells.](#) AP20187 was used to selectively ablate tumor-associated endothelial cells in xenograft tumors, via a caspase-based artificial death switch (iCaspase-9).

Kuenzel, S. *et al.* (2010) *J. Immunol.* **184**(4):1990–2000. [The nucleotide-binding oligomerization domain-like receptor NLRC5 is involved in IFN-dependent antiviral immune responses.](#) AP20187 was used to trigger dimerization and test the role of NLRC5 in the activation of signaling pathways that use the IFN-specific response element and IFN-gamma activation sequence.

Lee, D. C. *et al.* (2010) *Invest. Ophthalmol. Vis. Sci.* **51**(2):1066–1070. [Fourier domain optical coherence tomography as a noninvasive means for in vivo detection of retinal degeneration in \*Xenopus laevis\* tadpoles.](#) Transgenic *X. laevis* tadpoles expressing inducible caspase-9 (iCasp9) were treated with AP20187 to induce rod photoreceptor death.

Léveillé, F. *et al.* (2010) *J. Neurosci.* **30**(7):2623–2635. [Suppression of the intrinsic apoptosis pathway by synaptic activity.](#) Inducible caspase-9 and AP20187 were used to cause cell death in cortical neurons, indicating that pathways downstream of caspase-9 activation are not a significant aspect of the anti-apoptotic effects of synaptic activity.

Malzer, E. *et al.* (2010) *J. Cell Sci.* **123**(Pt 17):2892–2900. [Impaired tissue growth is mediated by checkpoint kinase 1 \(CHK1\) in the integrated stress response.](#) Activation of the integrated stress response kinase PERK by AP20187 repressed protein translation and resulted in a striking atrophic eye phenotype in *Drosophila melanogaster*.

Oberst, A. *et al.* (2010) *J. Biol. Chem.* **285**(22):16632–16642. [Inducible dimerization and inducible cleavage reveal a requirement for both processes in caspase-8 activation.](#) Unlike the executioner caspases, both dimerization and cleavage of caspase-8 are required to activate caspase-8 *in vitro* and apoptosis in cellular systems.

Pan, P.Y. *et al.* (2010) *Cancer Res.* **70**(1):99–108. [Immune stimulatory receptor CD40 is required for T-cell suppression and T regulatory cell activation mediated by myeloid-derived suppressor cells in cancer.](#) MaFIA transgenic mice were implanted intrahepatically with OVA-B16 tumor cells and treated with AP20187 to induce CD115-specific depletion. The results suggest that CD40 is essential for myeloid-derived suppressor cell-mediated immune suppression and for tumor-specific T-regulatory cell expansion.

Pond, A. C. *et al.* (2010) *Cancer Res.* **70**(12):4868–4879. [Fibroblast growth factor receptor signaling dramatically accelerates tumorigenesis and enhances oncoprotein translation in the mouse mammary tumor virus-Wnt-1 mouse model of breast cancer.](#) An inducible FGF receptor (iFGFR) activation with AP20187 dramatically enhanced mammary tumorigenesis in the mouse mammary tumor virus-Wnt-1 transgenic mouse.

Priceman, S. J. *et al.* (2010) *Blood* **115**(7):1461–1471. [Targeting distinct tumor-infiltrating myeloid cells by inhibiting CSF-1 receptor: combating tumor evasion of antiangiogenic therapy.](#) The MaFIA transgenic mouse model was used study the impact of macrophage ablation on tumor angiogenesis.

# Inducible Homodimerization Citations

## 2010 continued

Soetandyo, N. *et al.* (2010) *J. Cell Sci.* **123**(Pt 7):1031–1038. [Role of intramembrane charged residues in the quality control of unassembled T-cell receptor  \$\alpha\$ -chains at the endoplasmic reticulum.](#) Endoplasmic reticulum-associated degradation machinery is inefficient when coping with oligomerized substrates.

Stuffers, S. *et al.* (2010) *J. Histochem. Cytochem.* **58**(11):1025–1032. [Time-resolved ultrastructural detection of phosphatidylinositol 3-phosphate.](#) A monomeric dimerizable FYVE probe and rapalog-induced dimerization were used to follow the distribution of phosphatidylinositol 3-phosphate [PtdIns(3)P] at the ultrastructural level.

Sun, Y. *et al.* (2010) *J. Immunol.* **185**(7):4272–4283. [TLR4 and TLR5 on corneal macrophages regulate \*Pseudomonas aeruginosa\* keratitis by signaling through MyD88-dependent and -independent pathways.](#) Selective depletion of macrophages and dendritic cells (using MaFIA mice) resulted in diminished cytokine production and cellular infiltration to the corneal stroma, and unimpaired bacterial growth.

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.](#) Chemically induced dimeric “traps” for Dynll1 and Dynlt1 can rapidly inhibit dynein function. The design principle can be extended to other molecular complexes for *in vivo* studies.

Villasenor, A. *et al.* (2010) *Dis. Model Mech.* **3**(9–10):567–580. [Rgs16 and Rgs8 in embryonic endocrine pancreas and mouse models of diabetes.](#) The regulators of G protein signaling Rgs16 and Rgs8 are expressed in pancreatic progenitor and endocrine cells during development, then extinguished in adults, but reactivated in models of both type 1 and type 2 diabetes, including the PANIC-ATTAC transgenic mouse model under the control of AP20187.

Winkler, I. G. *et al.* (2010) *Blood* **116**(23):4815–4828. [Bone marrow macrophages maintain hematopoietic stem cell \(HSC\) niches and their depletion mobilizes HSCs.](#) Granulocyte colony-stimulating factor (G-CSF) mobilization rapidly depletes endosteal osteoblasts, suppressing endosteal bone formation and decreasing expression of factors required for hematopoietic stem cell (HSC) retention and self-renewal in macrophage Fas-induced apoptosis (MaFIA) mice.

Zhao, L. *et al.* (2010) *J. Biol. Chem.* **285**(4):2488–2497. [Dimerization of CPAP orchestrates centrosome cohesion plasticity.](#) HeLa cells expressing tFLAG-CPAP-FKBP were treated with AP20187 to study the role of CPAP dimerization in centrosome maintenance and cohesion, and in accurate cell division.

## 2009

Alfa, R. W., Tuszynski, M. H., and Blesch, A. (2009) *J. Neurosci. Res.* **87**(12):2624–2631. [A novel inducible tyrosine kinase receptor to regulate signal transduction and neurite outgrowth.](#) AP20187-induced dimerization of the intracellular domain of trkA can simulate the biological activity of NGF and regulate intracellular neurotrophin receptor signaling.

Chinnery, H. R. *et al.* (2009) *J. Immunol.* **182**(5):2738–2744. [Bone marrow chimeras and c-fms conditional ablation \(MaFIA\) mice reveal an essential role for resident myeloid cells in lipopolysaccharide/TLR4-induced corneal inflammation.](#) Corneas of MaFIA mice were stimulated with LPS and treated  $\pm$  AP20187 to understand the role of macrophages and dendritic cells in development of corneal inflammation.

Eggert, S. *et al.* (2009) *J. Biol. Chem.* **284**(42):28943–28952. [Induced dimerization of the amyloid precursor protein leads to decreased amyloid- \$\beta\$  protein production.](#) APP dimerization (induced by AP20187) directly affects gamma-secretase processing. Dimerization is not required for Abeta production.

Ezraty, E. J. *et al.* (2009) *J. Cell Biol.* **187**(5):733–747. [Clathrin mediates integrin endocytosis for focal adhesion disassembly in migrating cells.](#) AP20187 was used to crosslink and thereby disrupt clathrin function, inhibit focal adhesion disassembly, and decrease the rate of cell migration.

# Inducible Homodimerization Citations

## 2009 continued

Hamm, L. M., Tam, B. M., and Moritz, O. L. (2009) *Invest. Ophthalmol. Vis. Sci.* **50**(2):885–892. [Controlled rod cell ablation in transgenic \*Xenopus laevis\*](#). AP20187 was used to induce an apoptotic cascade, for an inducible model of rod cell death/retinitis pigmentosa.

Komarova, Y. *et al.* (2009) *J. Cell Biol.* **184**(5):691–706. [Mammalian end binding proteins control persistent microtubule growth](#). Dimerization is required for EB1 and EB3 to promote microtubule growth and suppress catastrophes.

Lin, J. H. *et al.* (2009) *PLoS ONE* **4**(1):e4170. [Divergent effects of PERK and IRE1 signaling on cell viability](#). Chemical-genetic strategies uncouple PERK and IRE1 activity from protein misfolding to determine their effects on cell viability.

Markey, K. A. *et al.* (2009) *Blood* **113**(22):5644–5649. [Conventional dendritic cells are the critical donor APC presenting alloantigen after experimental BMT](#). Conditional depletion of conventional dendritic cells (cDCs), plasmacytoid DC (pDCs), macrophages, or B cells was used to demonstrate that donor cDCs are the critical population presenting alloantigen after bone marrow transplantation.

Moseley, G. W. *et al.* (2009) *J. Cell Sci.* **122**(Pt 20):3652–3662. [Dual modes of rabies P-protein association with microtubules: a novel strategy to suppress the antiviral response](#). The oligomeric state of rabies virus P-protein regulates nuclear trafficking via microtubule-inhibited and microtubule-facilitated mechanisms.

Roostae, A., Côté, S., and Roucou X. (2009) *J. Biol. Chem.* **284**(45):30907–30916. [Aggregation and amyloid fibril formation induced by chemical dimerization of recombinant prion protein in physiological-like conditions](#). The authors treated a chimeric cellular protein (PrP(C)) with AP20187 to cause a rapid conformational change and simultaneous aggregation of the protein, suggesting that dimerization of PrP(C) may initiate the pathogenesis of prion diseases.

Xian, W. *et al.* (2009) *Cancer Res.* **69**(6):2244–2251. [Fibroblast growth factor receptor 1-transformed mammary epithelial cells are dependent on RSK activity for growth and survival](#). Conditional activation of FGFR1 results in cellular transformation marked by epidermal growth factor-independent cell growth, anchorage-independent cell proliferation and survival, loss of cell polarity, and epithelial-to-mesenchymal transition.

Zhang, X., Turner, C., and Godbey, W. T. (2009) *Mol. Biotechnol.* **41**(3):236–246. [Comparison of caspase genes for the induction of apoptosis following gene delivery](#). The expression of caspase 3 plus caspase 9 produced phosphatidylserine flipping in addition to fragmentation of genomic DNA. The delivery of a combination of caspase genes could be readily moved to in vivo research of bladder and colon cancer treatments, and holds great applicability to a wide array of additional tumor types.

## 2008

Abdel-Azim, H. *et al.* (2008) *Blood* **111**(8):4064–4074. [Expansion of multipotent and lymphoid-committed human progenitors through intracellular dimerization of Mpl](#). Intracellular dimerization of Mpl in target cells triggered by AP20187 was used to expand uncommitted and lymphoid-committed human hematopoietic progenitor cells *in vitro* or *in vivo*.

Chang, M. K. *et al.* (2008) *J. Immunol.* **181**(2):1232–1244. [Osteal tissue macrophages are intercalated throughout human and mouse bone lining tissues and regulate osteoblast function \*in vitro\* and \*in vivo\*](#). Depletion of resident bone macrophages *in vivo* in the MaFIA mouse caused complete loss of osteoblast bone-forming surface—implicating osteal macrophages, in addition to osteoclasts and osteoblasts, as principal participants in bone dynamics.

de Witte, M. A. *et al.* (2008) *J. Immunol.* **180**(9):6365–6373. [An inducible caspase 9 safety switch can halt cell therapy-induced autoimmune disease](#). An inducible caspase 9-based safety switch can be used to halt an ongoing immune attack in a murine model for cell therapy-induced type I diabetes.

# Inducible Homodimerization Citations

## 2008 continued

Guerrero, A. D., Chen, M., and Wang, J. (2008) *Apoptosis* **13**(1):177–186. [Delineation of the caspase-9 signaling cascade](#). Chemically induced dimerization was used to understand the order of caspase signaling during apoptosis.

Kwiatkowski, B. A. *et al.* (2008) *J. Cell Physiol.* **215**(3):803–817. [FGFR4 and its novel splice form in myogenic cells: Interplay of glycosylation and tyrosine phosphorylation](#). Induced homodimerization was used to study the function of FGFR4 in myogenic differentiation.

Miller, C. P., and Blau, C. A. (2008) *Gene Ther.* **15**(10):759–764. [Using gene transfer to circumvent off-target effects](#). A method for circumventing off-target effects using a conditionally active signaling protein activated by an exogenously administered synthetic ligand.

Mionnet, C., Bogliolo, S., and Arkowitz, R. A. (2008) *J. Biol. Chem.* **283**(25):17515–17530. [Oligomerization regulates the localization of Cdc24, the Cdc42 activator in \*Saccharomyces cerevisiae\*](#). Chemically induced oligomerization was used to determine that Cdc24p oligomerization regulates Cdc42p activation via its localization.

Oyadomari, S. *et al.* (2008) *Cell Metab.* **7**(6):520–532. [Dephosphorylation of translation initiation factor 2 \$\alpha\$  enhances glucose tolerance and attenuates hepatosteatosis in mice](#). Transgenic mice expressing the cytosolic PERK kinase domain fused to an artificial dimerization domain were treated with AP20187 to activate the integrated stress response in the liver.

Poliakov, A. *et al.* (2008) *J. Cell Biol.* **183**(5):933–947. [Regulation of EphB2 activation and cell repulsion by feedback control of the MAPK pathway](#). FGFR1 activation prevents segregation, repulsion, and collapse responses to ephrinB1 ligand.

Ranganathan, A. C. *et al.* (2008) *Cancer Res.* **68**(9):3260–3268. [Dual function of pancreatic endoplasmic reticulum kinase in tumor cell growth arrest and survival](#). Chemically induced pancreatic endoplasmic reticulum kinase (PERK) promotes survival *in vitro* and inhibits colon carcinoma growth *in vivo*.

Steel, C. D. *et al.* (2008) *Lab Anim. (NY)* **37**(1):26–32. [Comparison of the lateral tail vein and the retro-orbital venous sinus as routes of intravenous drug delivery in a transgenic mouse model](#). To compare lateral tail vein and retro-orbital venous sinus injections, MaFIA mice were injected with AP20187, and macrophage depletion was compared for the lung, spleen, bone marrow, and peritoneal exudate cells. Both injection routes were similarly effective.

Wang, Z. V. *et al.* (2008) *Diabetes* **57**(8):2137–2148. [PANIC-ATTAC: a mouse model for inducible and reversible  \$\beta\$ -cell ablation](#). PANIC-ATTAC (pancreatic islet beta-cell apoptosis through targeted activation of caspase 8) is a mouse model for inducible and reversible ablation of pancreatic beta-cells.

Xiang, B. *et al.* (2008) *Proc. Natl. Acad. Sci. USA* **105**(34):12463–12468. [Brk is coamplified with ErbB2 to promote proliferation in breast cancer](#). ErbB2 dimerization increases the intrinsic activity of Brk, a cytoplasmic tyrosine kinase, induces cell proliferation, and shortens the latency of ErbB2-induced tumors.

Zhang, X., Atala, A., and Godbey, W. T. (2008) *Cancer Gene Ther.* **15**(8):543–552. [Expression-targeted gene therapy for the treatment of transitional cell carcinoma](#). Chemically inducible forms of caspases 3 and 9 were used to reduce bladder mass tumor volume and angiogenesis, and to inhibit tumor growth.

# Inducible Homodimerization Citations

2007

Acevedo, V. D. *et al.* (2007) *Cancer Cell* **12**(6):559–571. [Inducible FGFR-1 activation leads to irreversible prostate adenocarcinoma and an epithelial-to-mesenchymal transition.](#) Activation of FGFR1 with chemical inducers of dimerization (CID) led to highly synchronous, step-wise progression to adenocarcinoma that is linked to an epithelial-to-mesenchymal transition (EMT) and implicated FGFR1 in prostate cancer progression.

Allocca, M. *et al.* (2007) *Invest. Ophthalmol. Vis. Sci.* **48**(11):5199–5206. [Constitutive and AP20187-induced Ret activation in photoreceptors does not protect from light-induced damage.](#) A chemical-induced GDNF receptor was activated with AP20187, in order to study the mechanism of GDNF action and its direct targets in the retina.

Chen, M. *et al.* (2007) *J. Biol. Chem.* **282**(46):33888–33895. [Caspase-9-induced mitochondrial disruption through cleavage of anti-apoptotic BCL-2 family members.](#) Chemically induced dimerization of caspase-9 was used to determine that caspase-9 induces feedback disruption of the mitochondrion through cleavage of Bcl-2, Bcl-xL, and Mcl-1.

Deng, Y. *et al.* (2007) *Am. J. Physiol. Cell Physiol.* **293**(4):C1404–C1411. [MEKK3 is required for endothelium function but is not essential for tumor growth and angiogenesis.](#) AP20187 was used to artificially activate Tie2 in either wild-type or MEKK3-deficient cells and determine that MEKK3 is critical for Ang1/Tie2 signaling to the p38 MAPK pathway.

Dong, Z. *et al.* (2007) *Exp. Cell Res.* **313**(16):3645–3657. [Level of endothelial cell apoptosis required for a significant decrease in microvessel density.](#) Inducible caspase-9 was used to understand the effects of endothelial cell apoptosis on blood vessel generation.

Gazdoiu, S. *et al.* (2007) *Mol. Cell Biol.* **27**(20):7041–7052. [Human Cdc34 employs distinct sites to coordinate attachment of ubiquitin to a substrate and assembly of polyubiquitin chains.](#) The chemical dimerizer AP20187 was used activate Cdc34 and study its role in polyubiquitination.

Goggin, K. *et al.* (2007) *J. Neurochem.* **102**(4):1195–1205. [Aggregation of cellular prion protein is initiated by proximity-induced dimerization.](#) Inducible oligomerization was used to test if, in the absence of any infectious prion particles, the encounter between PrP(C) molecules may trigger its aggregation in neuronal cells.

Isaacs, H. V. *et al.* (2007) *Biol. Cell* **99**(3):165–173. [FGF4 regulates blood and muscle specification in \*Xenopus laevis\*.](#) The authors used a drug inhibitor of FGF signalling and an inducible form of FGF receptor 1 to identify a period of competence during late blastula and gastrula stages when FGF signalling acts to regulate blood versus muscle specification.

Jin, H., and Wang, J. Y. (2007) *Mol. Biol. Cell* **18**(10):4143–4154. [Abl tyrosine kinase promotes dorsal ruffles but restrains lamellipodia extension during cell spreading on fibronectin.](#) Induced dimerization of the nonreceptor Abl tyrosine kinase, but not a kinase-defective version of Abl, inhibits cell spreading on fibronectin.

Lapteva, N. *et al.* (2007) *Cancer Res.* **67**(21):10528–10537. [Enhanced activation of human dendritic cells by inducible CD40 and Toll-like receptor-4 ligation.](#) The authors used a ligand-inducible CD40 receptor (iCD40) to achieve targeted, reversible activation of CD40 *in vivo*, bypassing the essential role of CD4(+) T cells in activating dendritic cells.

Miyake, Z. *et al.* (2007) *Mol. Cell Biol.* **27**(7):2765–2776. [Activation of MTK1/MEKK4 by GADD45 through induced N-C dissociation and dimerization-mediated trans autophosphorylation of the MTK1 kinase domain.](#) An inducible version of MTK1 was used to determine that GADD45 binding leads to the activation of the kinase catalytic domain of MTK1.

Niu, H. *et al.* (2007) *Mol. Cell Biol.* **27**(15):5456–5467. [Mek1 kinase is regulated to suppress double-strand break repair between sister chromatids during budding yeast meiosis.](#) Using a version of Mek1 that can be conditionally dimerized during meiosis, Mek1 function was shown to be promoted by dimerization, but DSBs and Mek1 recruitment to the meiosis-specific chromosomal core protein Red1 were also required for Mek1 activation.

# Inducible Homodimerization Citations

## 2007 continued

Nourse, M. B. *et al.* (2007) *Lab. Invest.* **87**(8):828–835. [Selective control of endothelial cell proliferation with a synthetic dimerizer of FGF receptor-1.](#) Human umbilical vein endothelial cells and human microvascular endothelial cells expressing an inducible FGF receptor were used to study the effects of synthetic receptor-dimerizing ligands.

Perez-Pinera, P. *et al.* (2007) *J. Biol. Chem.* **282**(39):28683–28690. [Anaplastic lymphoma kinase is activated through the pleiotrophin/receptor protein-tyrosine phosphatase  \$\beta/\zeta\$  signaling pathway: an alternative mechanism of receptor tyrosine kinase activation.](#) Phosphorylation of anaplastic lymphoma kinase (ALK) in PTN-stimulated cells is mediated through the PTN/RPTPbeta/zeta signaling pathway, through a unique alternative mechanism of RTK activation.

Quintarelli, C. *et al.* (2007) *Blood* **110**(8):2793–2802. [Co-expression of cytokine and suicide genes to enhance the activity and safety of tumor-specific cytotoxic T lymphocytes.](#) An inducible caspase-9 suicide gene increased the safety and feasibility of adoptively transferred tumor-specific CTLs.

Sequeira, S. J. *et al.* (2007) *PLoS ONE* **2**(7):e615. [Inhibition of proliferation by PERK regulates mammary acinar morphogenesis and tumor formation.](#) An inducible version of the ER kinase PERK was used to study PERK's role in limiting MCF10A mammary epithelial cell proliferation during acinar morphogenesis in 3D Matrigel culture as well as in preventing mammary tumor formation *in vivo*.

Shah, V. R. *et al.* (2007) *Genesis* **45**(4):194–199. [Double-inducible gene activation system for caspase 3 and 9 in epidermis.](#) The authors developed a double inducible model containing both RU486 and AP20187, which in addition to inducing caspase activation, has potential applicability specifically to other genes encoding proteins that require a dimerization event for activation.

Song, G. J., Jones, B. W., and Hinkle, P. M. (2007) *Proc. Natl. Acad. Sci. USA* **104**(46):18303–18308. [Dimerization of the thyrotropin-releasing hormone receptor potentiates hormone-dependent receptor phosphorylation.](#) Regulated receptor dimerization increases thyrotropin-releasing hormone induced receptor endocytosis.

Stevens, K. R. *et al.* (2007) *Hum. Gene Ther.* **18**(5):401–412. [Chemical dimerization of fibroblast growth factor receptor-1 induces myoblast proliferation, increases intracardiac graft size, and reduces ventricular dilation in infarcted hearts.](#) An AP20187-inducible version of fibroblast growth factor receptor-1 (iFGFR-1) to achieve targeted graft cell proliferation.

Tokuo, H., Mabuchi, K., and Ikebe, M. (2007) *J. Cell Biol.* **179**(2):229–238. [The motor activity of myosin-X promotes actin fiber convergence at the cell periphery to initiate filopodia formation.](#) Using a dimer-inducing technique, the authors show that the motor function of myoX, and not the cargo function, is critical for initiating filopodia formation.

Winter, S. F. *et al.* (2007) *Oncogene* **26**(34):4897–4907. [Conditional activation of FGFR1 in the prostate epithelium induces angiogenesis with concomitant differential regulation of Ang-1 and Ang-2.](#) The authors used a transgenic mouse model, JOCK-1, to follow spontaneous angiogenesis in a conditional autochthonous system.

Xian, W., Schwertfeger, K. L., and Rosen, J. M. (2007) *Mol. Endocrinol.* **21**(4):987–1000. [Distinct roles of fibroblast growth factor receptor 1 and 2 in regulating cell survival and epithelial-mesenchymal transition.](#) A chemically inducible FGFR (iFGFR) dimerization system was combined with an *in vitro* three-dimensional HC11 mouse mammary epithelial cell culture model in order to examine the separate roles of FGFR1 and FGFR2 signaling in polarized epithelia.

# Inducible Homodimerization Citations

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Aranda, V. *et al.* (2006) *Nat. Cell Biol.* **8**(11):1235–1245. [Par6-aPKC uncouples ErbB2 induced disruption of polarized epithelial organization from proliferation control.](#) Oncogenes target polarity proteins, to disrupt glandular organization and protect cells from apoptotic death during development of carcinoma.

Bashamboo, A. *et al.* (2006) *J. Cell Sci.* **119**(Pt 15):3039–3046. [The survival of differentiating embryonic stem cells is dependent on the SCF-KIT pathway.](#) Studies the function of the stem cell factor receptor KIT in embryonic stem cells by introducing an AP20187-inducible receptor into Kit-null cells.

Baumeister, M. A. *et al.* (2006) *Biochem. J.* **400**(3):563–572. [The Dbs PH domain contributes independently to membrane targeting and regulation of guanine nucleotide-exchange activity.](#) Dimerization of a Dbs DH/PH domain fragment is sufficient to drive it to the plasma membrane.

Blau, C. A. and Peterson, K. R. (2006) *Methods Mol. Biol.* **349**:163–173. [Establishment of cell lines that exhibit correct ontogenic stage-specific gene expression profiles from tissues of yeast artificial chromosome transgenic mice using chemically induced growth signals.](#) A derivative of the thrombopoietin receptor (mpl) was used to bring the proliferative status of primary BM marrow cells under the control of a chemical inducer of dimerization (CID).

Burnett, S. H. *et al.* (2006) *J. Surg. Res.* **131**(2):296–301. [Development of peritoneal adhesions in macrophage depleted mice.](#) Develops a mouse model to study the induction and repair of peritoneal adhesions based on the finding that such adhesions develop upon AP20187-mediated depletion of macrophages in MaFIA mice.

Clackson, T. (2006) *Chem. Biol. Drug Des.* **67**(6):440–442. [Dissecting the Functions of Proteins and Pathways using Chemically Induced Dimerization.](#) Review of the ARGENT and RPD chemically-controlled dimerization systems.

Fooksman, D. R. *et al.* (2006) *J. Immunol.* **176**(11):6673–6680. [Clustering class I MHC modulates sensitivity of T cell recognition.](#) Uses AP20187-mediated dimerization to show that clustering of class I MHC molecules on the surface of B lymphoblasts enhances their recognition by T cells.

Fukada, M. *et al.* (2006) *FEBS Lett.* **580**(17):4051–4056. [Protein tyrosine phosphatase receptor type Z is inactivated by ligand-induced oligomerization.](#) Uses AP20187 to demonstrate that a protein tyrosine phosphatase receptor is inactivated by oligomerization.

Goffin, L. *et al.* (2006) *Mol. Biol. Cell* **17**(12):5309–5323. [The unfolded protein response transducer Ire1p contains a nuclear localization sequence recognized by multiple  \$\beta\$  importins.](#) AP20187 was used to dimerize the Ire1p transmembrane receptor kinase/endonuclease, which transduces the unfolded protein response (UPR) from the endoplasmic reticulum (ER) to the nucleus in *Saccharomyces cerevisiae*.

Hirate, Y. and Okamoto, H. (2006) *Curr. Biol.* **16**(4):421–427. [Canopy1, a Novel Regulator of FGF Signaling around the Midbrain-Hindbrain Boundary in Zebrafish.](#) Uses AP20187-induced dimerization of FGFR1 to demonstrate that expression of Canopy1 is essential for normal FGF signaling in zebrafish embryos. The inducible FGFR1 gene was injected as mRNA into a specific area of the brain and AP20187 was added directly to the embryos.

Marciniak, S. J. *et al.* (2006) *J. Cell Biol.* **172**(2):201–209. [Activation-dependent substrate recruitment by the eukaryotic translation initiation factor 2 kinase PERK.](#) Uses AP20187-mediated oligomerization of PERK to study its mechanism of activation and downstream signalling.

Nagasawa, Y. *et al.* (2006) *Stem Cells* **24**(4):908–917. [Anatomical compartments modify the response of human hematopoietic cells to a mitogenic signal.](#) Uses AP20187-mediated oligomerization of mpl to drive expansion of human cord blood CD34+ cells transplanted into mice. The engineered cells' response to the mitogenic signal is influenced by the anatomical compartment in which they reside.

# Inducible Homodimerization Citations

## 2006 continued

Pelletier, L. *et al.* (2006) *Cancer Res.* **66**(7):3681–3687.  [\$\gamma\$ -secretase-dependent proteolysis of CD44 promotes neoplastic transformation of rat fibroblastic cells.](#) Uses AP20187-controlled homodimerization of Ret to show that Ret-driven neoplastic transformation correlates with increased expression and subsequent cleavage of CD44.

Pinsky, M. S. *et al.* (2006) *J. Dent. Res.* **85**(5):436–441. [Activation of iCaspase-9 in neovessels inhibits oral tumor progression.](#) Uses AP20187-mediated dimerization to show that activation of caspase-9 in neovascular endothelial cells is sufficient to inhibit growth of oral tumors xenografted into mice.

Schwertfeger, K. L. *et al.* (2006) *Cancer Res.* **66**(11):5676–5685. [A critical role for the inflammatory response in a mouse model of preneoplastic progression.](#) Transgenic mice expressing an AP20187-inducible fibroblast growth factor receptor-1 (iFGFR1) were used to examine role of the microenvironment in early stages of tumorigenesis. These mice were also crossed with MaFIA mice to study the effects of macrophage depletion on iFGFR1-mediated phenotypes.

Sun, M. *et al.* (2006) *J. Immunol.* **177**(3):1481–1491. [The cytoplasmic domain of Fas ligand costimulates TCR signals.](#) Oligomerization of the FasL cytoplasmic domain is sufficient for FasL-mediated costimulation of T cells.

Umeda, K. *et al.* (2006) *Cell* **126**(4):741–754. [ZO-1 and ZO-2 independently determine where claudins are polymerized in tight-junction strand formation.](#) When a truncated version of the tight junction protein ZO-1 was forcibly recruited to lateral membranes and dimerized, claudins were dramatically polymerized.

Weinreich, M. A. *et al.* (2006) *Blood* **108**(12):3713–3721. [Growth factor receptors as regulators of hematopoiesis.](#) Conditional derivatives of fibroblast growth factor receptor-1 and the thrombopoietin receptor act as hematopoietic regulators and possess activities that growth factors do not.

Witt, A. E. *et al.* (2006) *J. Proteome Res.* **5**(3):599–610. [Functional proteomics approach to investigate the biological activities of cDNAs implicated in breast cancer.](#) The functional activity of a subset of the Breast Cancer 1000 collection was evaluated in cell-based assays that monitor changes in cell proliferation, migration, and morphogenesis in MCF-10A mammary epithelial cells expressing a variant of ErbB2 that can be inducibly activated through dimerization.

Xiao, H. *et al.* (2006) *J. Biomol. Screen.* **11**(3):225–235. [Establishment of a Cell Model Based on FKBP12 Dimerization for Screening of FK506-like Neurotrophic Small Molecular Compounds.](#) The AP20187-mediated homodimerization system was used to screen for novel FK506-like small molecules. Compounds were screened for the ability to block apoptosis caused by forced dimerization of mBax.

Zhan, L., Xiang, B., and Muthuswamy, S. K. (2006) *Cancer Res.* **66**(10):5201–5208. [Controlled activation of ErbB1/ErbB2 heterodimers promote invasion of three-dimensional organized epithelia in an ErbB1-dependent manner: implications for progression of ErbB2-overexpressing tumors.](#) Uses AP1510-mediated homodimerization and AP21967-mediated heterodimerization to compare the tumor-promoting activities of ErbB2 homodimers and ErbB1-ErbB2 heterodimers.

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- Abell, A. N. and Johnson, G. L. (2005) *J. Biol. Chem.* **280**(43):35793–35796. [MEKK4 is an effector of the embryonic TRAF4 for JNK activation.](#) Uses AP20187 to show that oligomerization of MEKK4 is sufficient to activate JNK.
- Blau, C. A. *et al.* (2005) *J. Biol. Chem.* **280**(44):36642–36647.  [\$\gamma\$ -Globin gene expression in chemical inducer of dimerization \(CID\)-dependent multi-potential cells established from human  \$\beta\$ -globin locus yeast artificial chromosome \( \$\beta\$ -YAC\) transgenic mice.](#) Developed cells that can be used to screen for inducers of gamma-globulin expression by using an AP20187-inducible mpl construct to drive proliferation of bone marrow cells derived from beta-YAC transgenic mice.
- Carlotti, F. *et al.* (2005) *Cancer Gene Ther.* **12**(7):627–639. [Development of an inducible suicide gene system based on human caspase 8.](#) Control of caspase 8 oligomerization allows for tightly regulated induction of apoptosis.
- Cheng, J. *et al.* (2005) *J. Biol. Chem.* **280**(14):13477–13482. [Dimerization through the catalytic domain is essential for MEKK2 activation.](#) Uses AP20187 to demonstrate that oligomerization of MEKK2 leads to its activation.
- Emery, D. W. *et al.* (2005) *Blood Cells Mol. Dis.* **34**(3):235–247. [Selection with a regulated cell growth switch increases the likelihood of expression for a linked  \$\gamma\$ -globin gene.](#) *In vivo* expansion of hematopoietic stem cells using the AP20187-inducible Mpl growth switch increases expression of a linked gamma-globin gene.
- Freche, B. *et al.* (2005) *J. Biol. Chem.* **280**(44):36584–36591. [Inducible dimerization of RET reveals a specific AKT deregulation in oncogenic signaling.](#) Uses AP20187-mediated dimerization to study downstream effects of activating the receptor tyrosine kinase RET.
- Gazdoiu, S. *et al.* (2005) *Proc. Natl. Acad. Sci. USA* **102**(42):15053–15058. [Proximity-induced activation of human Cdc34 through heterologous dimerization.](#) Demonstrates that AP20187-mediated dimerization of Cdc34 (overexpressed and purified from insect cells) is sufficient to activate its catalytic activity.
- Gouzi, J. Y. *et al.* (2005) *J. Cell Sci.* **118**(Pt 24):5811–5823. [Role of the subcellular localization of ALK tyrosine kinase domain in neuronal differentiation of PC12 cells.](#) Uses AP20187 to control the dimerization and activation of the membrane tyrosine kinase ALK.
- Hanks, B. A. *et al.* (2005) *Nat. Med.* **11**(2):130–137. [Re-engineered CD40 receptor enables potent pharmacological activation of dendritic-cell cancer vaccines \*in vivo\*.](#) Dendritic cell activation mediated by an AP20187-inducible CD40 receptor results in more potent T-cell effector responses in mice and may lead to more potent human cancer vaccines.
- Harding, H. P. *et al.* (2005) *Cell Metab.* **2**(6):361–371. [Bioactive small molecules reveal antagonism between the integrated stress response and sterol-regulated gene expression.](#) Uses AP20187-inducible PERK to examine the role that phosphorylation eIF2 alpha plays in the inhibition of sterol regulatory element binding protein target genes.
- Karpova, A. Y. *et al.* (2005) *Neuron* **48**(5):727–735. [Rapid and reversible chemical inactivation of synaptic transmission in genetically targeted neurons.](#) Describes the development of dimerization-based switches, called MISTs, for reversible inactivation of neurotransmitter release.
- Kobinger, G. P. *et al.* (2005) *Mol. Ther.* **11**(1):105–111. [Pharmacologically regulated regeneration of functional human pancreatic islets.](#) A method was developed to stimulate proliferation of insulin secreting beta-cells *in vitro* and *in vivo* using an AP20187-inducible Epo receptor.
- Larrivee, B. *et al.* (2005) *J. Immunol.* **175**(5):2890–2899. [Minimal contribution of marrow-derived endothelial precursors to tumor vasculature.](#) Uses an AP20187-inducible VEGF receptor 2 to demonstrate that the VEGFR-2 pathway is not sufficient for the recruitment and/or expansion of endothelial progenitor cells in mice.

# Inducible Homodimerization Citations

## 2005 continued

Larrivee, B., Pollet, I., and Karsan, A. (2005) *J. Immunol.* **175**(5):3015–3024. [Activation of vascular endothelial growth factor receptor-2 in bone marrow leads to accumulation of myeloid cells: role of granulocyte-macrophage colony-stimulating factor.](#) Uses an AP20187-inducible VEGF receptor 2 to demonstrate that the VEGFR-2 pathway induces expansion of myeloid cells in mice.

Lupo, G. *et al.* (2005) *Development* **132**(7):1737–1748. [Dorsoventral patterning of the \*Xenopus\* eye: a collaboration of Retinoid, Hedgehog and FGF receptor signaling.](#) Uses an AP20187-inducible FGF receptor 1 to explore the role of the FGFR1 signaling pathway in dorsoventral patterning of the *Xenopus* eye.

Nikitina, E. Y. *et al.* (2005) *Cancer Res.* **65**(10):4309–4319. [Versatile prostate cancer treatment with inducible caspase and interleukin-12.](#) Further explored the use of AP20187-mediated oligomerization of caspase-1 to induce tumor cell apoptosis in a mouse prostate cancer model.

Pajvani, U. B. *et al.* (2005) *Nat. Med.* **11**(7):797–803. [Fat apoptosis through targeted activation of caspase 8: a new mouse model of inducible and reversible lipoatrophy.](#) Describes the generation of transgenic mice expressing an FKBP-caspase 8 fusion protein that allows selective elimination of adipocytes by administration of AP20187.

Reginato, M. J. *et al.* (2005) *Mol. Cell Biol.* **25**(11):4591–4601. [Bim regulation of lumen formation in cultured mammary epithelial acini is targeted by oncogenes.](#) Uses AP1510-mediated oligomerization of ErbB2 to study the role of Bim in the regulation of lumen formation.

Siatskas, C. *et al.* (2005) *FASEB J.* **19**(12):1752–1754. [Specific pharmacological dimerization of KDR in lentivirally transduced human hematopoietic cells activates antiapoptotic and proliferative mechanisms.](#) Uses AP20187 to study the function of a KDR/flk-1/VEGFR-2 chimeric receptor using functional, biochemical and microarray analyses.

Song, G. J. and Hinkle, P. M. (2005) *Mol. Endocrinol.* **19**(11):2859–2870. [Regulated Dimerization of the Thyrotropin-Releasing Hormone Receptor Affects Receptor Trafficking but Not Signaling.](#) Uses AP20187 to examine the effect that dimerization has on the trafficking of the thyrotropin-releasing hormone receptor, a G protein-coupled receptor.

Song, W. *et al.* (2005) *Gene Ther.* **12**(4):320–329. [Antiangiogenic gene therapy: disruption of neovascular networks mediated by inducible caspase-9 delivered with a transcriptionally targeted adenoviral vector.](#) Delivery of an AP20187-inducible caspase-9 to endothelial cells of mice results in disruption of neovascularization.

Storez, H. *et al.* (2005) *J. Biol. Chem.* **280**(48):40210–40215. [Homo- and hetero-oligomerization of  \$\beta\$ -arrestins in living cells.](#) AP20187-mediated homodimerization of GFP-labelled beta arrestin 2 demonstrates that the pre-oligomerized protein has unchanged intracellular translocation kinetics and behavior compared to the undimerized protein.

Straathof, K. C. *et al.* (2005) *Blood* **105**(11):4247–4254. [An inducible caspase 9 safety switch for T-cell therapy.](#) AP20187-inducible caspase-9 can lead to the selective elimination of 99% of transduced T cells *in vivo*, suggesting promise as a safety switch for human T-cell therapies.

Trujillo, M. E., Pajvani, U. B., and Scherer, P. E. (2005) *Cell Cycle* **4**(9):1141–1145. [Apoptosis Through Targeted Activation of Caspase8 \(“ATTAC-mice”\): Novel Mouse Models of Inducible and Reversible Tissue Ablation.](#) Use of the AP20187 system to develop mouse models in which specific cell types can be inducibly eliminated via caspase-8 dimerization.

# Inducible Homodimerization Citations

## 2005 continued

Van Stry, M. *et al.* (2005) *Proc. Natl. Acad. Sci. USA* **102**(23):8233–8238. [Distinct effectors of platelet-derived growth factor receptor- \$\alpha\$  signaling are required for cell survival during embryogenesis.](#) Uses AP1510-mediated dimerization of PDGFR-alpha to study the effectors of its activity in *Xenopus* embryos.

Xian, W. *et al.* (2005) *J. Cell Biol.* **171**(4):663–673. [Pleiotropic effects of FGFR1 on cell proliferation, survival, and migration in a 3D mammary epithelial cell model.](#) Drug-inducible FGFR1 causes rapid loss of polarity, reinitiation of proliferation, and reduction of luminal cell apoptosis in an *in vitro* 3-D HC11 mouse mammary epithelial cell model, followed by invasion of cells into the surrounding matrix and EMT.

## 2004

Berger, C. *et al.* (2004) *Blood* **103**(4):1261–1269. [Pharmacologically regulated Fas-mediated death of adoptively transferred T cells in a nonhuman primate model.](#) Demonstrates that the AP1903-inducible Fas-based suicide switch can be employed to regulate the survival of adoptively transferred T cells in non-human primates.

Brouckaert, G. *et al.* (2004) *Mol. Biol. Cell* **15**(3):1089–1100. [Phagocytosis of necrotic cells by macrophages is phosphatidyserine dependent and does not induce inflammatory cytokine production.](#) Uses AP1510-mediated oligomerization of an FKBP-FADD fusion protein to induce necrotic cell death.

Burnett, S. H. *et al.* (2004) *J. Leukoc. Biol.* **75**(4):612–623. [Conditional macrophage ablation in transgenic mice expressing a Fas-based suicide gene.](#) Describes the generation of MaFIA transgenic mice, which express an AP20187-inducible Fas death switch selectively in macrophages and dendritic cells.

Cotugno, G. *et al.* (2004) *Hum. Gene Ther.* **15**(11):1101–1108. [Pharmacological regulation of the insulin receptor signaling pathway mimics insulin action in cells transduced with viral vectors.](#) A system for pharmacologic regulation of the insulin signaling pathway is described based on AP20187-mediated oligomerization of the insulin receptor.

Deng, J. *et al.* (2004) *Mol. Cell Biol.* **24**(23):10161–10168. [Translational repression mediates activation of nuclear factor kappa B by phosphorylated translation initiation factor 2.](#) Uses AP20187-mediated activation of PERK to establish a role for eIF2-alpha phosphorylation in NF-kappaB activation.

Iwamoto, K. *et al.* (2004) *Biochem. Biophys. Res. Commun.* **325**(1):229–234. [Dimer formation of receptor activator of nuclear factor kappaB induces incomplete osteoclast formation.](#) AP20187-mediated dimerization of the RANK receptor induces a subset of the activities induced by the RANK ligand induced trimerization.

Karlsson, T., Henriksson, R., and Hedman, H. (2004) *J. Neurooncol.* **66**(1–2):71–79. [Induction of apoptosis in resistant glioma cells by synthetic caspase-activation.](#) Uses AP20187-inducible FADD and caspases 3 and 8 to delineate the molecular basis of apoptosis resistance of several glioma cell lines.

Lu, P. D. *et al.* (2004) *EMBO J.* **23**(1):169–179. [Cytoprotection by pre-emptive conditional phosphorylation of translation initiation factor 2.](#) Uses AP20187-mediated oligomerization to study the activity of PERK, independent of upstream stress signaling.

Mikolajczyk, J. *et al.* (2004) *Biochemistry* **43**(22):10560–10569. [Activation and substrate specificity of caspase-14.](#) Studies the role of dimerization in controlling caspase-14 activity, using the AP20187-mediated homodimerization system.

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Nam, Y. J. *et al.* (2004) *Mol. Cell* **15**(6):901–912. [Inhibition of both the extrinsic and intrinsic death pathways through nonhomotypic death-fold interactions.](#) AP20187-mediated dimerization decreases ARC's ability to inhibit apoptosis.

Richard, R. E. *et al.* (2004) *Blood* **103**(12):4432–4439. [Modulating erythrocyte chimerism in a mouse model of pyruvate kinase deficiency.](#) AP20187-mediated oligomerization of mpl is used to show that expansion of donor red blood cells can improve inherited anemia and reduce abnormal erythropoiesis in mice.

Richard, R. E. *et al.* (2004) *Mol. Ther.* **10**(4):730–740. [Differences in F36VMpl-based \*in vivo\* selection among large animal models.](#) AP20187-mediated oligomerization of mpl leads to only a modest expansion of hematopoietic cells in baboons, in contrast to what was seen previously in mice.

Seton-Rogers, S. E. *et al.* (2004) *Proc. Natl. Acad. Sci. USA* **101**(5):1257–1262. [Cooperation of the ErbB2 receptor and transforming growth factor  \$\beta\$  in induction of migration and invasion in mammary epithelial cells.](#) Describes the results of a screen for genes that induce migration of cells already activated by AP1510-mediated dimerization of ErbB2.

Strasser, V. *et al.* (2004) *Mol. Cell Biol.* **24**(3):1378–1386. [Receptor Clustering Is Involved in Reelin Signaling.](#) AP20187-mediated dimerization of Dab1 is sufficient to induce its phosphorylation.

Tognon, C. E. *et al.* (2004) *Mol. Cell Biol.* **24**(11):4636–4650. [Mutations in the SAM domain of the ETV6-NTRK3 chimeric tyrosine kinase block polymerization and transformation activity.](#) Uses AP20187 to show that oligomerization of NTRK3 is not sufficient to transform cells.

Vanden Berghe, T. *et al.* (2004) *J. Biol. Chem.* **279**(9):7925–7933. [Differential signaling to apoptotic and necrotic cell death by Fas-associated death domain protein FADD.](#) Uses AP1510-mediated oligomerization to study the role of FADD in apoptotic and necrotic signaling pathways.

Wang, S. *et al.* (2004) *Proc. Natl. Acad. Sci. USA* **101**(14):4833–4838. [QSulf1, a heparan sulfate 6-O-endosulfatase, inhibits fibroblast growth factor signaling in mesoderm induction and angiogenesis.](#) Uses AP20187-mediated oligomerization of FGFR1 to study its function in *Xenopus* embryos.

Zhao, S. *et al.* (2004) *Mol. Ther.* **10**(3):456–468. [In vivo selection of genetically modified erythroid cells using a jak2-based cell growth switch.](#) Demonstrates that AP20187-mediated oligomerization of Jak2 acts as an erythroid-specific cell growth switch upon transduction of murine marrow cells in mice.

## 2003

Arias-Salgado, E. G. *et al.* (2003) *Proc. Natl. Acad. Sci. USA* **100**(23):13298–13302. [Src kinase activation by direct interaction with the integrin  \$\beta\$  cytoplasmic domain.](#) Uses AP1510 to show that Src can be activated via beta3 integrin clustering.

Arya, M. *et al.* (2003) *J. Thromb. Haemost.* **1**(6):1150–1157. [Glycoprotein Ib-IX-mediated activation of integrin  \$\alpha\_{IIb}\beta\_3\$ : effects of receptor clustering and von Willebrand factor adhesion.](#) AP20187-mediated dimerization of glycoprotein Ib-IX increases the strength of its interaction with the von Willebrand factor.

Berger, C. *et al.* (2003) *Blood* **101**(2):476–484. [CD28 costimulation and immunoaffinity-based selection efficiently generate primary gene-modified T cells for adoptive immunotherapy.](#) Describes the development of a strategy to generate large numbers of T cells transduced with a retroviral vector encoding a dimerizer-activated Fas-based suicide gene, and characterization of the functionality of the resulting cells.

# Inducible Homodimerization Citations

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Buensuceso, C., de Virgilio, M., and Shattil, S. J. (2003) *J. Biol. Chem.* **278**(17):15217–15224. [Detection of integrin  \$\alpha\_{IIb}\beta\_3\$ -clustering in living cells.](#) Uses AP1510 to study the clustering of integrin  $\alpha_{IIb}\beta_3$  induced by intracellular events.

Carlson, J. C. *et al.* (2003) *J. Am. Chem. Soc.* **125**(6):1501–1507. [Designing protein dimerizers: the importance of ligand conformational equilibria.](#) Theoretical, biophysical, and structural analysis of a methotrexate homodimerizer.

Chang, D. W. *et al.* (2003) *J. Biol. Chem.* **278**(19):16466–16469. [Oligomerization is a general mechanism for the activation of apoptosis initiator and inflammatory procaspases.](#) Uses AP20187 to demonstrate that both initiator and inflammatory caspases are activated by oligomerization.

Chang, D. W. *et al.* (2003) *EMBO J.* **22**(16):4132–4142. [Interdimer processing mechanism of procaspase-8 activation.](#) Uses AP20187 to reveal key dimerization-based steps that lead to the activation of procaspase-8.

Chang, D. W. and Yang, X. (2003) *Sci. STKE* **2003**(167):PL1. [Activation of procaspases by FK506 binding protein-mediated oligomerization.](#) Protocols for dimerizer-inducible apoptosis of mammalian cells using FKBP-caspase-8 fusion proteins and AP20187.

Dowds, T. A., *et al.* (2003) *Biochem. Biophys. Res. Commun.* **302**(3):575–580. [Regulation of cryopyrin/Pypaf1 signaling by pyrin, the familial Mediterranean fever gene product.](#) Studies using the homodimerizer AP1510 reveal interactions between cryopyrin and ASC that lead to apoptosis.

Freeman, K. W. *et al.* (2003) *Cancer Res.* **63**(19):6237–6243. [Conditional activation of fibroblast growth factor receptor \(FGFR\) 1, but not FGFR2, in prostate cancer cells leads to increased osteopontin induction, extracellular signal-regulated kinase activation, and \*in vivo\* proliferation.](#) Uses an AP20187-inducible FGFR1 to demonstrate its role in signaling and its ability to promote growth of prostate tumor cells *in vivo*.

Freeman, K. W. *et al.* (2003) *Cancer Res.* **63**(23):8256–8263. [Inducible prostate intraepithelial neoplasia with reversible hyperplasia in conditional FGFR1-expressing mice.](#) Uses transgenic mice containing an AP20187-inducible FGFR1 to show that the development and progression of key pathologic changes seen in early-stage prostate cancer are directly dependent on FGFR1 activation.

Godbey, W. T. and Atala, A. (2003) *Gene Ther.* **10**(17):1519–1527. [Directed apoptosis in Cox-2-overexpressing cancer cells through expression-targeted gene delivery.](#) AP20187-inducible caspase-3 (or -9) was used to selectively induce apoptosis in tumor cells that overexpress Cox-2, including cells that are typically resistant to apoptosis.

Junker, K. *et al.* (2003) *Gene Ther.* **10**(14):1189–1197. [Kinetics of cell death in T lymphocytes genetically modified with two novel suicide fusion genes.](#) Demonstrates the efficient and rapid induction of apoptosis in T cells upon AP20187-mediated oligomerization of the death effector domain of FADD.

Kazansky, A. V., Spencer, D. M., and Greenberg, N. M. (2003) *Cancer Res.* **63**(24):8757–62. [Activation of signal transducer and activator of transcription 5 is required for progression of autochthonous prostate cancer: evidence from the transgenic adenocarcinoma of the mouse prostate system.](#) An AP20187-inducible version of a naturally occurring dominant-negative isoform of STAT5B was used to block the invasive potential of prostate cells.

Larrivee, B. *et al.* (2003) *J. Biol. Chem.* **278**(24):22006–22013. [Vascular endothelial growth factor receptor-2 induces survival of hematopoietic progenitor cells.](#) Uses AP20187 to dimerize the intracellular domain of the VEGF receptor-2 to demonstrate its role in maintaining survival of hematopoietic progenitor cells.

# Inducible Homodimerization Citations

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Lee, L. A., Van Hoewyk, D., and Orr-Weaver, T. L. (2003) *J. Genes Dev.* **17**(23):2979–2991. [The \*Drosophila\* cell cycle kinase PAN GU forms an active complex with PLUTONIUM and GNU to regulate embryonic divisions.](#) Uses an AP20187-inducible form of the *Drosophila* protein PLU to study the mechanism of activation of an associated kinase.

Martin, M. E. *et al.* (2003) *Cancer Cell* **4**(3):197–207. [Dimerization of MLL fusion proteins immortalizes hematopoietic cells.](#) Demonstrates that AP20187-mediated dimerization of an MLL fusion protein converts it into a transcriptional transactivator and is sufficient to immortalize cells in a reversible manner.

Masumoto, J. *et al.* (2003) *Biochem. Biophys. Res. Commun.* **303**(1):69–73. [ASC is an activating adaptor for NF-kappa B and caspase-8-dependent apoptosis.](#) Demonstrates that AP1510-induced oligomerization of the caspase recruitment domain of either ASC or Ipaf induces apoptosis and NF-kappaB activation.

Masumoto, J. *et al.* (2003) *J. Biol. Chem.* **278**(6):4268–4276. [Caspy, a zebrafish caspase, activated by ASC oligomerization is required for pharyngeal arch development.](#) AP1510-mediated oligomerization of ASC is sufficient to activate the Zebrafish caspase, Caspy.

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