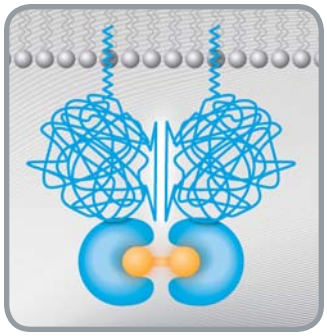
Inducible Homodimerization Citations

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



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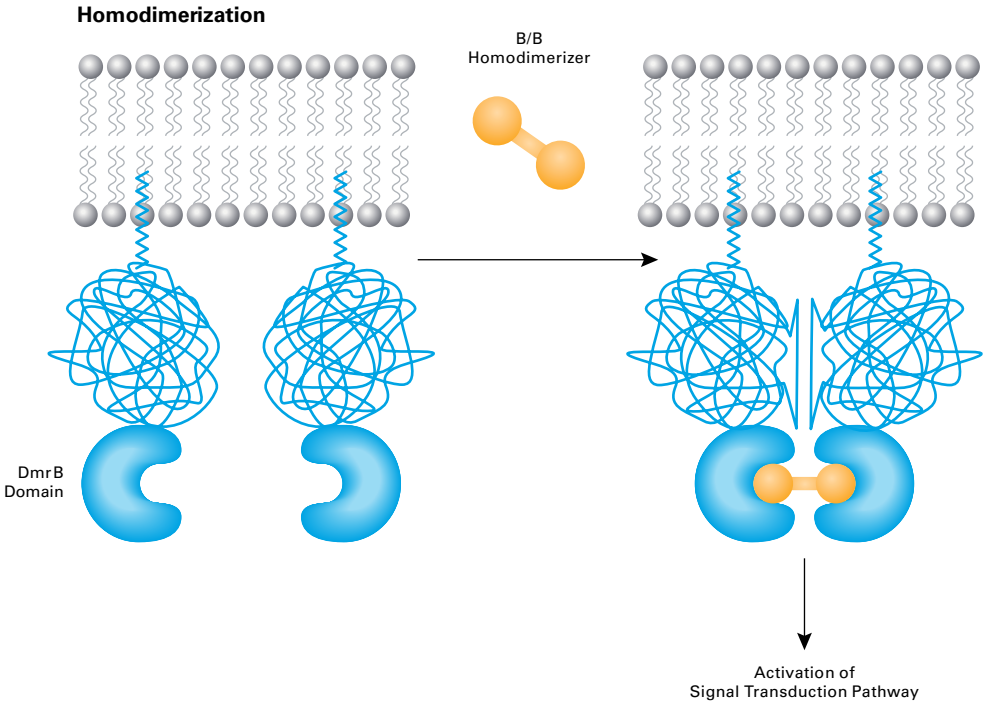

Fusion proteins containing the DmrB domain do not interact until the B/B Homodimerizer is added. This cell-permeable ligand induces the fusion proteins to interact, activating downstream signaling in real time. This example shows activation of a signal transduction pathway through dimerization of a membrane-bound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

Products

ARIAD/ARGENT Product	Clontech Product	Cat. #	Package Size
ARGENT Regulated Homodimerization Kit	iDimerize Inducible Homodimer System	635068	each
	Lenti-X™ iDimerize Inducible Homodimer System	635072	each
AP20187	B/B Homodimerizer	635060 635059 635058 635069	500 µl 5 x 500 µl 5 mg 25 mg

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.

2012 Citations

Liu, J. *et al.* (2012) *Nucleic Acids Res.* [Epub ahead of print] Structural mechanism of the phosphorylation-dependent dimerization of the MDC1 forkhead-associated domain. MDC1 mutants in which the FHA domain is deleted or impaired in its ability to dimerize form fewer foci at DNA damage sites. The localization defect is largely rescued by an AP20187-mediated dimerization module.

Muñoz, N. M. *et al.* (2012) *Nucleic Acids Res.* **40**(2):e14. Novel reporter systems for facile evaluation of I-SceI-mediated genome editing. The authors developed a reporter system that utilizes an inducible Caspase-9 suicide gene to identify and select cells that undergo targeted gene repair and to minimize random integrations and non-homologous end-joining events.

O'Brien, J. *et al.* (2012) *Development* **139**(2):269–275. Macrophages are crucial for epithelial cell death and adipocyte repopulation during mammary gland involution. The MaFIA mouse model was used to deplete macrophages expressing colony stimulating factor 1 receptor during weaning-induced mammary gland involution.

Wang, Y. *et al.* (2012) *Science Signaling* **5**(207):ra6. Plexins are GTPase-activating proteins for Rap and are activated by induced dimerization. The RapGAP activity of plexins was activated by AP20187-induced dimerization; defining a pathway for plexin signaling and providing insights into the mechanism for semaphorin-induced activation of plexins that could be exploited in regenerative therapies for axon-severing injuries.

2011 Citations

Avivar-Valderas, A. *et al.* (2011) *Mol. Cell. Biol.* **31**(17):3616–3629. PERK integrates autophagy and oxidative stress responses to promote survival during ECM detachment. Inducible activation of an Fv2E-ΔNPERK chimera resulted in lumen-filled mammary epithelial acini.

Bade, L. K. *et al.* (2011) *J. Cell Sci.* **124**(Pt 18):3106–3117. Mammary tumorigenesis induced by fibroblast growth factor receptor 1 requires activation of the epidermal growth factor receptor. Dimerization and activation of iFGFR1 by AP20187 (the B/B Homodimerizer) activated the same signaling pathways as endogenous FGFR1 and led to an increase in cellular migration, proliferation and signaling.

Cheng, Q. *et al.* (2011) *Mol. Cell. Biol.* **31**(24):4951–4963. Regulation of MDM2 E3 ligase activity by phosphorylation after DNA damage. AP20187-induced oligomerization of MDM2 partially overcame the inhibitory effect of ATM-mediated phosphorylation of the upstream sequence and stimulated p53 ubiquitination.

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.

Delarosa, S. *et al.* (2011) *Am. J. Physiol. Renal Physiol.* **301**(3):F554–564. Activity of the Ste20-like kinase, SLK, is enhanced by homodimerization. Homodimerization of an SLK fusion protein increased the activation-specific phosphorylation of proapoptotic kinases and enhanced apoptosis.

Fischer-Posovszky, P. *et al.* (2011) *Endocrinology* **152**(8):3074–3081. Targeted deletion of adipocytes by apoptosis leads to adipose tissue recruitment of alternatively activated m2 macrophages. The degree and type of inflammatory response upon ablation of live adipocytes have been studied through AP20187-mediated activation of Caspase-8 in a FAT-ATTAC mouse model.

Gao, N. *et al.* (2011) *Mol. Biol. Cell* **22**(17):2994–3009 Mannose-6-phosphate regulates destruction of lipid-linked oligosaccharides. AP20187-mediated dimerization of the IRE1 alpha cytosolic unit activated glycogenolysis, releasing mannose-6-phosphate and causing lipid-linked oligosaccharide destruction, suggesting a novel mammalian stress-signaling pathway.

Hwang, Y. *et al.* (2011) *Mol. Cancer Res.* **9**(9):1199–1208. Forced dimerization increases the activity of DeltaEGFR/EGFRvIII and enhances its oncogenicity. AP20187-induced dimerization of chimeric ΔEGFR significantly increased the intensity of its signal, suggesting that the naturally occurring ΔEGFR does not form strong or stable dimers as part of its low level signal. Forced dimerization enhanced the oncogenic signal of the receptor, implying that the ΔEGFR is a potent oncogene despite, not because of, its low intensity.

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.

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*.

2011 Citations…continued

Luhovy, A.Y. *et al.* (2011) *J. Biol. Chem.* [Epub ahead of print]. Regulation of the STE20-like kinase, SLK: Involvement of activation segment phosphorylation. To test whether homodimerization of SLK affects phosphorylation, Fv-SLK 1-373 WT was treated with AP20187 to induce regulated dimerization.

Matsui, T. *et al.* (2011) *Proc. Natl. Acad. Sci. USA* **108**(24):9881–9886. Canopy1, a positive feedback regulator of FGF signaling, controls progenitor cell clustering during Kupffer's vesicle organogenesis. AP20187-mediated conditional activation of FGFR1 in dorsal forerunner cells of zebrafish led to a 67% reduction in the broken-up dorsal forerunner cells phenotype relative to vehicle (ethanol)-treated controls, suggesting a regulatory mechanism underlying cell cluster formation, which is an indispensable step for formation of a functional Kupffer's vesicle and establishment of the left–right asymmetric body plan.

Ngo, M. C. *et al.* (2011) *Hum. Mol. Genet.* **20**(R1):R93–99. *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.* **19**(7):1287–1294. 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.

Ouda, R. *et al.* (2011) *J. Biol. Chem.* **286**(29):26210–26219. Retinoic acid-inducible gene I-inducible miR-23b inhibits infections by minor group rhinoviruses through down-regulation of the very low density lipoprotein receptor. AP20187-mediated oligomerization of the CARD of RIG-I resulted in signaling, activating the IFN-beta and IL-6 genes.

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 dimerization 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.* **79**(5):1842–1847. 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.

Suzuki, M. *et al.* (2011) *J. Biol. Chem.* **286**(34):29964–29972. Attenuated CagA oncoprotein in *Helicobacter pylori* from Amerindians in Peruvian Amazon. Strains of *H. pylori* from Amerindians from the remote Peruvian Amazon contain novel alleles of cagA, a major virulence gene, and reveal distinctive properties of their encoded CagA proteins. The Amerindian CagA proteins behave as dominant negative inhibitors of prototype CagA during mixed infection of Mongolian gerbils, but the inhibitory effect is avoided when CagA is forcibly premultimerized using AP20187.

Tseng, H-C. *et al.* (2011) *Anticancer Res.* **31**(12):4239–4249. Cytoskeleton network and cellular migration modulated by nuclear-localized receptor tyrosine kinase ROR1. Activation of FKBP-fused ROR1 with AP20187 led to a significant increase in actin stress fibers and increased cellular migration.

Zlatic, S. A. *et al.* (2011) *Mol. Biol. Cell* **22**(10):1699–1715. 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 Citations

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):39481–34989. 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.

2010 Citations…continued

Jiang, Z. *et al.* (2010) *J. Neurosci.* **30**(7):2582–2594. eIF2α 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), activated 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.

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 α-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.

2010 Citations…continued

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 Citations

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 ± 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-β protein production. APP dimerization (induced by AP20187) directly affects gamma-secretase processing. Dimerization is not required for Abeta production.

Ezratty, 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.

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 bone marrow transplantation. 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.

Roostaee, 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 Citations

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 a 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.

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 2a 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 β-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.

2007 Citations

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.

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