

# [Editorial: adam10 in cancer immunology and autoimmunity: more than a simple bioch...](https://assignbuster.com/editorial-adam10-in-cancer-immunology-and-autoimmunity-more-than-a-simple-biochemical-scissor/)

[Health & Medicine](https://assignbuster.com/essay-subjects/health-n-medicine/)

Editorial on the Research Topic
[ADAM10 in Cancer Immunology and Autoimmunity: More Than a Simple Biochemical Scissor](https://www.frontiersin.org/research-topics/10945/adam10-in-cancer-immunology-and-autoimmunity-more-than-a-simple-biochemical-scissor)

Altered expression of the ADAM (A Disintegrin and Metalloproteinase) proteins, usually involved in biological processes such as proteolysis, cell adhesion, proliferation, migration, and signaling, has been associated with several diseases including asthma, arthritis, neurodegenerative diseases, atherosclerosis, and cancer ( [1](#B1) – [4](#B4) ). Also, ADAM10 is involved in the pathogenesis of autoimmune diseases such as multiple sclerosis or systemic lupus erythematosus, and the development of inflammation or allergy ( [5](#B5) , [6](#B6) ). This Special Issue is focused on the pathophysiological role of ADAM10 in tumors and autoimmunity, including potential therapeutic targeting of this enzyme with specific inhibitors.

The best-characterized function of ADAM10 is the proteolytic cleavage of different transmembrane proteins, a process known as “ ectodomain shedding” that targets the extracellular domain of several types of cell surface molecules ( [1](#B1) , [2](#B2) ). Other functions of this enzyme are not directly related to the activation of its catalytic domain but rather due to its exosite, that is a secondary substrate-binding site ( [7](#B7) ).

In particular, ADAM10 has been reported to shed the “ stress-induced” molecules MICA, MICB, and ULBPs expressed on the cancer cell surface ( [8](#B8) – [11](#B11) ). These molecules are responsible for inducing an immune response against cancer cells upon binding to NKG2D receptors that are expressed on natural killer (NK) cells and most cytotoxic T lymphocytes. The ADAM10-mediated proteolytic shedding of these NKG2D ligands (NKG2DL) into the extracellular milieu can impair the recognition of cancer cells by T or NK cells ( [9](#B9) – [11](#B11) ). This mechanism has been evidenced in many types of tumors including melanoma, various carcinomas, and hematopoietic malignancies such as chronic lymphocytic leukemia, acute myeloid leukemia, non-Hodgkin and Hodgkin's lymphomas ( [12](#B12) , [13](#B13) ). In the latter neoplasia, ADAM10-mediated CD30 shedding is reported to impair the recognition of this molecule by therapeutic monoclonal antibodies, in addition to the reduced immune surveillance through enhanced NKG2DL shedding ( [12](#B12) – [14](#B14) ).

The contribution by [Zingoni et al.](https://doi.org/10.3389/fimmu.2020.00447) provides a topical overview of the tumor-associated up-regulation of NKG2DL and the cell stress-regulated ADAM10 activity mediating NKG2DL shedding in the context of carcinogenesis and cancer therapy. They highlight enhanced NKG2DL shedding in response to chemotherapy-induced cellular senescence of tumor cells as a consequence of both, induced NKG2DL expression and ADAM10 activity. Similarly, therapeutic targeting of the DNA damage response (DDR) affects the release of soluble NKG2DL by tumor cells through induction of NKG2DL and modulating ADAM10 expression and activity. They emphasize that targeting ADAM-mediated shedding of NKG2DL in the course of cancer therapies may restore immune detection and elimination of tumor cells via the NKG2D axis.

[Hansen et al.](https://doi.org/10.3389/fimmu.2020.00398) explain how CD30 processing, due to the activity of ADAM10, might influence the impact of CD30 antibody-drug conjugates, such as Brentuximab Vedotin, reducing their efficacy in Hodgkin lymphomas, as previously described by the same group. This review evidences that the enzyme is catalytically active in extracellular vesicles and gradually releases sCD30, that can be measured in the patients' plasma, creating a “ crossfire effect” that may modulate the response to therapy ( [16](#B16) ).

In turn, [Maurer et al.](https://doi.org/10.3389/fimmu.2020.00044) point out a peculiar function of platelet-associated ADAM10. ADAM10 is highly expressed by platelets, where it is not only of major relevance in regulating hemostasis but also appears to contribute to the metastasis-promoting effect of platelets. This review comprehensively lists ADAM10 target structures of platelets and discusses various modes of ADAM10-mediated shedding including canonical shedding (in cis) and non-canonical shedding (in trans). Further, the authors summarize new insights into the world of proteins involved in ADAM10 processing, trafficking, and modulation such as TspanC8 tetraspanins, as reported by others ( [15](#B15) ), and TIMPs. Overall, this review illustrates the multifaceted role of ADAM10 expressed by platelets.

For all these reasons, in the last decade, an increasing interest has emerged toward the development of selective ADAMs ligands for their potential use for early-stage diagnosis and therapy of cancer ( [16](#B16) – [19](#B19) ). Several ADAM10 inhibitors proved to be effective in reducing tumor cell growth, inducing anti-tumor immune reactions or enhancing the effect of therapeutic antibody-drug conjugates *in vitro* . Examples are given by studies in gliomas, solid cancers, and hematologic tumors, including Hodgkin lymphoma ( [14](#B14) , [20](#B20) – [24](#B24) ).

Some recent ADAM10 blockers proved to rescue both anti-tumor effect of Brentuximab Vedotin and sensitivity of Reed-Sternberg cells to effector lymphocytes, in particular through the antibody-dependent cellular cytotoxicity elicited by the therapeutic monoclonal antibody Iratumumab ( [20](#B20) – [24](#B24) ). Interestingly, these inhibitors were also carried by exosomes, making them able to spread their effects into the microenvironment ( [24](#B24) ). This points to the importance of targeting ADAM10 on different cell types, since exosomes can be released, for instance, by mesenchymal stromal cells or fibroblasts or accessory cells at the site of the lesion ( [24](#B24) , [25](#B25) ). Very recently, cleavage of PD-L1 from lymphoma and solid tumor cells by ADAM10 and ADAM17 has been reported ( [26](#B26) , [27](#B27) ). The consequent release of soluble PD-L1 was shown to induce apoptosis of immunocompetent CD8 T cells leading to an impairment of the anti-tumor immune response ( [27](#B27) ). This mechanism may confer resistance to PD-(L)1 blockers, thereby playing a role in tumor-mediated immunosuppression. Hence, it is conceivable to consider ADAM10/17 inhibitors also for an improvement of immunotherapies targeting the PD-1/PD-L1 axis.

However, despite the considerable number of studies generating significant data, the clinical trials have not confirmed the initial encouraging results and effective compounds are still missing.

The contributions by [Smith et al.](https://doi.org/10.3389/fimmu.2020.00499) and by [Minond et al.](https://doi.org/10.3389/fmolb.2020.00075) face this problem from two different viewpoints. The former reports on recent pre-clinical data with inhibitors and clinical data supporting the use of ADAM10 inhibitors in cancer and autoimmunity, searching for a mean to improve the potency and efficiency of anti-ADAM10 products alone or paired with other drug treatments ( [Smith et al.](https://doi.org/10.3389/fimmu.2020.00499) ). The latter introduces the importance of ADAM10 non-catalytic domain, called exosite, addressing the possibility to target the exosite and, in particular, the glycosylation sites of ADAM10 ( [Minond](https://doi.org/10.3389/fmolb.2020.00075) ). This suggests that proteolysis of specific ADAM10 substrates involved in various diseases can be targeted using knowledge on their glycosylation as well as on differences in their non-catalytic domains ( [28](#B28) , [29](#B29) ). These results may open new avenues to circumvent the poor selectivity of inhibitors for ADAM10 and/or for ADAM10 substrates that currently represents the main obstacle to develop efficient drugs. Such novel targeting concepts introduce a new perspective for therapeutic approaches involving ADAM10 inhibitors in a wide spectrum of diseases.

## Author Contributions

MZ, AR, AP, and AS planned, wrote, and revised the editorial manuscript. All authors contributed to the article and approved the submitted version.

## Funding

This work was partly supported by funds from the Italian Ministry of Health 5x1000 2015-2016 to AP, AIRC IG-17074 to MZ.

## Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## References

1. Reiss K, Saftig P. The “ A Disintegrin And Metalloprotease” (ADAM) family of sheddases: physiological and cellular functions. *Semin Cell Dev Biol* . (2009) 20: 126–37. doi: 10. 1016/j. semcdb. 2008. 11. 002

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/19049889) | [CrossRef Full Text](https://doi.org/10.1016/j.semcdb.2008.11.002) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=K.+Reiss&author=P.+Saftig+&publication_year=2009&title=The+“ A+Disintegrin+And+Metalloprotease”+(ADAM)+family+of+sheddases%3A+physiological+and+cellular+functions&journal=Semin+Cell+Dev+Biol&volume=20&pages=126-37)

2. Saftig P, Lichtenthaler SF. The alpha secretase ADAM10: a metalloprotease with multiple functions in the brain. *Prog Neurobiol.* (2015) 135: 1–20. doi: 10. 1016/j. pneurobio. 2015. 10. 003

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26522965) | [CrossRef Full Text](https://doi.org/10.1016/j.pneurobio.2015.10.003) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=P.+Saftig&author=SF.+Lichtenthaler+&publication_year=2015&title=The+alpha+secretase+ADAM10%3A+a+metalloprotease+with+multiple+functions+in+the+brain&journal=Prog+Neurobiol.&volume=135&pages=1-20)

3. Duffy MJ, McKiernan E, O'Donovan N, McGowan P. Role of ADAMs in cancer formation and progression. *Clin Cancer Res.* (2009) 15: 1140–4. doi: 10. 1158/1078-0432. CCR-08-1585

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/19228719) | [CrossRef Full Text](https://doi.org/10.1158/1078-0432.CCR-08-1585) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=MJ.+Duffy&author=E.+McKiernan&author=N.+O'Donovan&author=P.+McGowan+&publication_year=2009&title=Role+of+ADAMs+in+cancer+formation+and+progression&journal=Clin+Cancer+Res.&volume=15&pages=1140-4)

4. Murphy G. The ADAMs: signalling scissors in the tumor microenvironment. *Nat Rev Cancer.* (2008) 8: 929–41. doi: 10. 1038/nrc2459

[CrossRef Full Text](https://doi.org/10.1038/nrc2459) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=G.+Murphy+&publication_year=2008&title=The+ADAMs%3A+signalling+scissors+in+the+tumor+microenvironment&journal=Nat+Rev+Cancer.&volume=8&pages=929-41)

5. Lambrecht BN, Vanderkerken M, Hammad H. The emerging role of ADAM metalloproteinases in immunity. *Nat Rev Immunol.* (2018) 18: 745–58. doi: 10. 1038/s41577-018-0068-5

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/30242265) | [CrossRef Full Text](https://doi.org/10.1038/s41577-018-0068-5) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=BN.+Lambrecht&author=M.+Vanderkerken&author=H.+Hammad+&publication_year=2018&title=The+emerging+role+of+ADAM+metalloproteinases+in+immunity&journal=Nat+Rev+Immunol.&volume=18&pages=745-58)

6. Gibb DR, Saleem SJ, Chaimowitz NS, Mathews J, Conrad DH. The emergence of ADAM10 as a regulator of lymphocyte development and autoimmunity. *Mol Immunol.* (2011) 48: 1319–27. doi: 10. 1016/j. molimm. 2010. 12. 005

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/21236490) | [CrossRef Full Text](https://doi.org/10.1016/j.molimm.2010.12.005) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=DR.+Gibb&author=SJ.+Saleem&author=NS.+Chaimowitz&author=J.+Mathews&author=DH.+Conrad+&publication_year=2011&title=The+emergence+of+ADAM10+as+a+regulator+of+lymphocyte+development+and+autoimmunity&journal=Mol+Immunol.&volume=48&pages=1319-27)

7. Dreymueller D, Ludwig A. Considerations on inhibition approaches for proinflammatory functions of ADAM proteases. *Platelets.* (2017) 28: 354–61. doi: 10. 1080/09537104. 2016. 1203396

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/27460023) | [CrossRef Full Text](https://doi.org/10.1080/09537104.2016.1203396) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=D.+Dreymueller&author=A.+Ludwig+&publication_year=2017&title=Considerations+on+inhibition+approaches+for+proinflammatory+functions+of+ADAM+proteases&journal=Platelets.&volume=28&pages=354-61)

8. Waldhauer I, Goehlsdorf D, Gieseke F, Weinschenk T, Wittenbrink M, Ludwig A, et al. Tumor-associated MICA is shed by ADAM proteases. *Cancer Res.* (2008) 68: 6368–76. doi: 10. 1158/0008-5472. CAN-07-6768

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/18676862) | [CrossRef Full Text](https://doi.org/10.1158/0008-5472.CAN-07-6768) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=I.+Waldhauer&author=D.+Goehlsdorf&author=F.+Gieseke&author=T.+Weinschenk&author=M.+Wittenbrink&author=A.+Ludwig+&publication_year=2008&title=Tumor-associated+MICA+is+shed+by+ADAM+proteases&journal=Cancer+Res.&volume=68&pages=6368-76)

9. Groh V, Wu J, Yee C, Spies T. Tumour-derived soluble MIC ligands impair expression of NKG2D and T-cell activation. *Nature.* (2002) 419: 734–8. doi: 10. 1038/nature01112

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/12384702) | [CrossRef Full Text](https://doi.org/10.1038/nature01112) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=V.+Groh&author=J.+Wu&author=C.+Yee&author=T.+Spies+&publication_year=2002&title=Tumour-derived+soluble+MIC+ligands+impair+expression+of+NKG2D+and+T-cell+activation&journal=Nature.&volume=419&pages=734-8)

10. Salih HR, Rammensee HG, Steinle A. Cutting edge: down-regulation of MICA on human tumors by proteolytic shedding. *J Immunol.* (2002) 169: 4098–102. doi: 10. 4049/jimmunol. 169. 8. 4098

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/12370336) | [CrossRef Full Text](https://doi.org/10.4049/jimmunol.169.8.4098) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=HR.+Salih&author=HG.+Rammensee&author=A.+Steinle+&publication_year=2002&title=Cutting+edge%3A+down-regulation+of+MICA+on+human+tumors+by+proteolytic+shedding&journal=J+Immunol.&volume=169&pages=4098-102)

11. Salih HR, Antropius H, Gieseke F, Lutz SZ, Kanz L, Rammensee HG, et al. Functional expression and release of ligands for the activating immunoreceptor NKG2D in leukemia. *Blood.* (2003) 102: 1389–96. doi: 10. 1182/blood-2003-01-0019

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/12714493) | [CrossRef Full Text](https://doi.org/10.1182/blood-2003-01-0019) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=HR.+Salih&author=H.+Antropius&author=F.+Gieseke&author=SZ.+Lutz&author=L.+Kanz&author=HG.+Rammensee+&publication_year=2003&title=Functional+expression+and+release+of+ligands+for+the+activating+immunoreceptor+NKG2D+in+leukemia&journal=Blood.&volume=102&pages=1389-96)

12. Zocchi MR, Catellani S, Canevali P, Tavella S, Garuti A, Villaggio B, et al. High ERp5/ADAM10 expression in lymph node microenvironment and impaired NKG2D-ligands recognition in Hodgkin lymphomas. *Blood.* (2012) 119: 1479–89. doi: 10. 1182/blood-2011-07-370841

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/22167753) | [CrossRef Full Text](https://doi.org/10.1182/blood-2011-07-370841) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=MR.+Zocchi&author=S.+Catellani&author=P.+Canevali&author=S.+Tavella&author=A.+Garuti&author=B.+Villaggio+&publication_year=2012&title=High+ERp5%2FADAM10+expression+in+lymph+node+microenvironment+and+impaired+NKG2D-ligands+recognition+in+Hodgkin+lymphomas&journal=Blood.&volume=119&pages=1479-89)

13. Chitadze G, Lettau M, Bhat J, Wesch D, Steinle A, Fürst D, et al. Shedding of endogenous MHC class I-related chain molecules A and B from different human tumor entities: heterogeneous involvement of the “ a disintegrin and metalloproteases” 10 and 17. *Int J Cancer* . (2013) 133: 1557–66. doi: 10. 1002/ijc. 28174

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/23526433) | [CrossRef Full Text](https://doi.org/10.1002/ijc.28174) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=G.+Chitadze&author=M.+Lettau&author=J.+Bhat&author=D.+Wesch&author=A.+Steinle&author=D.+Fürst+&publication_year=2013&title=Shedding+of+endogenous+MHC+class+I-related+chain+molecules+A+and+B+from+different+human+tumor+entities%3A+heterogeneous+involvement+of+the+“ a+disintegrin+and+metalloproteases”+10+and+17&journal=Int+J+Cancer&volume=133&pages=1557-66)

14. Eichenauer DA, Simhadri VL, von Strandmann EP, Ludwig A, Matthews V, Reiners KS, et al. ADAM10 inhibition of human CD30 shedding increases specificity of targeted immunotherapy *in vitro* . *Cancer Res.* (2007) 67: 332–8. doi: 10. 1158/0008-5472. CAN-06-2470

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/17210715) | [CrossRef Full Text](https://doi.org/10.1158/0008-5472.CAN-06-2470) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=DA.+Eichenauer&author=VL.+Simhadri&author=EP.+von+Strandmann&author=A.+Ludwig&author=V.+Matthews&author=KS.+Reiners+&publication_year=2007&title=ADAM10+inhibition+of+human+CD30+shedding+increases+specificity+of+targeted+immunotherapy+in+vitro&journal=Cancer+Res.&volume=67&pages=332-8)

15. Matthews AL, Szyroka J, Collier R, Noy PJ, Tomlinson MG. Scissor sisters: regulation of ADAM10 by the TspanC8 tetraspanins. *Biochem Soc Trans.* (2017) 45: 719–30. doi: 10. 1042/BST20160290

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28620033) | [CrossRef Full Text](https://doi.org/10.1042/BST20160290) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=AL.+Matthews&author=J.+Szyroka&author=R.+Collier&author=PJ.+Noy&author=MG.+Tomlinson+&publication_year=2017&title=Scissor+sisters%3A+regulation+of+ADAM10+by+the+TspanC8+tetraspanins&journal=Biochem+Soc+Trans.&volume=45&pages=719-30)

16. Duffy MJ, Mullooly M, O'Donovan N, Sukor S, Crown J, Pierce A, et al. The ADAMs family of proteases: new biomarkers and therapeutic targets for cancer? *Clin Proteomics.* (2011) 8: 9–13. doi: 10. 1186/1559-0275-8-9

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/21906355) | [CrossRef Full Text](https://doi.org/10.1186/1559-0275-8-9) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=MJ.+Duffy&author=M.+Mullooly&author=N.+O'Donovan&author=S.+Sukor&author=J.+Crown&author=A.+Pierce+&publication_year=2011&title=The+ADAMs+family+of+proteases%3A+new+biomarkers+and+therapeutic+targets+for+cancer%3F&journal=Clin+Proteomics.&volume=8&pages=9-13)

17. Saftig P, Reiss K. The “ A Disintegrin And Metalloproteases” ADAM10 and ADAM17: novel drug targets with therapeutic potential? *Eur J Cell Biol* . (2011) 90: 527–35. doi: 10. 1016/j. ejcb. 2010. 11. 005

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/21194787) | [CrossRef Full Text](https://doi.org/10.1016/j.ejcb.2010.11.005) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=P.+Saftig&author=K.+Reiss+&publication_year=2011&title=The+“ A+Disintegrin+And+Metalloproteases”+ADAM10+and+ADAM17%3A+novel+drug+targets+with+therapeutic+potential%3F&journal=Eur+J+Cell+Biol&volume=90&pages=527-35)

18. Wetzel S, Seipold L, Saftig P. The metalloproteinase ADAM10: a useful therapeutic target? *Biochim Biophys Acta Mol Cell Res.* (2017) 1864(11 Pt B): 2071–81. doi: 10. 1016/j. bbamcr. 2017. 06. 005

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28624438) | [CrossRef Full Text](https://doi.org/10.1016/j.bbamcr.2017.06.005) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=S.+Wetzel&author=L.+Seipold&author=P.+Saftig+&publication_year=2017&title=The+metalloproteinase+ADAM10%3A+a+useful+therapeutic+target%3F&journal=Biochim+Biophys+Acta+Mol+Cell+Res.&volume=1864&pages=2071-81)

19. Poggi A, Zocchi MR. How to exploit stress-related immunity against Hodgkin's lymphoma: targeting ERp5 and ADAM sheddases. *Oncoimmunol.* (2013) 2: e27089. doi: 10. 4161/onci. 27089

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/24498565) | [CrossRef Full Text](https://doi.org/10.4161/onci.27089) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=A.+Poggi&author=MR.+Zocchi+&publication_year=2013&title=How+to+exploit+stress-related+immunity+against+Hodgkin's+lymphoma%3A+targeting+ERp5+and+ADAM+sheddases&journal=Oncoimmunol.&volume=2&pages=e27089)

20. Zocchi MR, Camodeca C, Nuti E, Rossello A, Venè R, Tosetti F, et al. (2016) ADAM10 new selective inhibitors reduce NKG2D ligand release sensitizing Hodgkin lymphoma cells to NKG2D-mediated killing. *Oncoimmunology* . (2015) 5: e1123367. doi: 10. 1080/2162402X. 2015. 1123367

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/27467923) | [CrossRef Full Text](https://doi.org/10.1080/2162402X.2015.1123367) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=MR.+Zocchi&author=C.+Camodeca&author=E.+Nuti&author=A.+Rossello&author=R.+Venè&author=F.+Tosetti+&publication_year=2015&title=(2016)+ADAM10+new+selective+inhibitors+reduce+NKG2D+ligand+release+sensitizing+Hodgkin+lymphoma+cells+to+NKG2D-mediated+killing&journal=Oncoimmunology&volume=5&pages=e1123367)

21. Camodeca C, Nuti E, Tepshi L, Boero S, Tuccinardi T, Stura EA. Discovery of a new selective inhibitor of A Disintegrin And Metalloprotease 10 (ADAM10) able to reduce the shedding of NKG2D ligands in Hodgkin's lymphoma cell models. *Eur J Med Chem.* (2016) 111: 193–201. doi: 10. 1016/j. ejmech. 2016. 01. 053

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/26871660) | [CrossRef Full Text](https://doi.org/10.1016/j.ejmech.2016.01.053) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=C.+Camodeca&author=E.+Nuti&author=L.+Tepshi&author=S.+Boero&author=T.+Tuccinardi&author=EA.+Stura+&publication_year=2016&title=Discovery+of+a+new+selective+inhibitor+of+A+Disintegrin+And+Metalloprotease+10+(ADAM10)+able+to+reduce+the+shedding+of+NKG2D+ligands+in+Hodgkin's+lymphoma+cell+models&journal=Eur+J+Med+Chem.&volume=111&pages=193-201)

22. Pham DH, Kim JS, Kim SK, Shin DJ, Uong NT, Hyun H, et al. Effects of ADAM10 and ADAM17 inhibitors on natural killer cell expansion and antibody-dependent cellular cytotoxicity against breast cancer cells. *In Vitro. Anticancer Res.* (2017) 37: 5507–13. doi: 10. 21873/anticanres. 11981

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28982863) | [CrossRef Full Text](https://doi.org/10.21873/anticanres.11981) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=DH.+Pham&author=JS.+Kim&author=SK.+Kim&author=DJ.+Shin&author=NT.+Uong&author=H.+Hyun+&publication_year=2017&title=Effects+of+ADAM10+and+ADAM17+inhibitors+on+natural+killer+cell+expansion+and+antibody-dependent+cellular+cytotoxicity+against+breast+cancer+cells&journal=In+Vitro.+Anticancer+Res.&volume=37&pages=5507-13)

23. Venkatesh HS, Tam LT, Woo PJ, Lennon J, Nagaraja S, Gillespie SM, et al. Targeting neuronal activity-regulated neuroligin-3 dependency in high-grade glioma. *Nature.* (2017) 549: 533–7. doi: 10. 1038/nature24014

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28959975) | [CrossRef Full Text](https://doi.org/10.1038/nature24014) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=HS.+Venkatesh&author=LT.+Tam&author=PJ.+Woo&author=J.+Lennon&author=S.+Nagaraja&author=SM.+Gillespie+&publication_year=2017&title=Targeting+neuronal+activity-regulated+neuroligin-3+dependency+in+high-grade+glioma&journal=Nature.&volume=549&pages=533-7)

24. Tosetti F, Venè R, Camodeca C, Nuti E, Rossello A, D'Arrigo C, et al. Specific ADAM10 inhibitors localize in exosome-like vesicles released by Hodgkin lymphoma and stromal cells and prevent sheddase activity carried to bystander cells. *Oncoimmunology.* (2018) 7: e1421889. doi: 10. 1080/2162402X. 2017. 1421889

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/29721369) | [CrossRef Full Text](https://doi.org/10.1080/2162402X.2017.1421889) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=F.+Tosetti&author=R.+Venè&author=C.+Camodeca&author=E.+Nuti&author=A.+Rossello&author=C.+D'Arrigo+&publication_year=2018&title=Specific+ADAM10+inhibitors+localize+in+exosome-like+vesicles+released+by+Hodgkin+lymphoma+and+stromal+cells+and+prevent+sheddase+activity+carried+to+bystander+cells&journal=Oncoimmunology.&volume=7&pages=e1421889)

25. Hansen HP, Trad A, Dams M, Zigrino P, Moss M, Tator M, et al. CD30 on extracellular vesicles from malignant Hodgkin cells supports damaging of CD30 ligand-expressing bystander cells with Brentuximab-Vedotin, *in vitro* . *Oncotarget.* (2016) 7: 30523–35. doi: 10. 18632/oncotarget. 8864

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/27105521) | [CrossRef Full Text](https://doi.org/10.18632/oncotarget.8864) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=HP.+Hansen&author=A.+Trad&author=M.+Dams&author=P.+Zigrino&author=M.+Moss&author=M.+Tator+&publication_year=2016&title=CD30+on+extracellular+vesicles+from+malignant+Hodgkin+cells+supports+damaging+of+CD30+ligand-expressing+bystander+cells+with+Brentuximab-Vedotin,+in+vitro&journal=Oncotarget.&volume=7&pages=30523-35)

26. Romero Y, Wise R, Zolkiewska A. Proteolytic processing of PD-L1 by ADAM proteases in breast cancer cells. *Cancer Immunol Immunother.* (2020) 69: 43. doi: 10. 1007/s00262-019-02437-2

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/31796994) | [CrossRef Full Text](https://doi.org/10.1007/s00262-019-02437-2) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=Y.+Romero&author=R.+Wise&author=A.+Zolkiewska+&publication_year=2020&title=Proteolytic+processing+of+PD-L1+by+ADAM+proteases+in+breast+cancer+cells&journal=Cancer+Immunol+Immunother.&volume=69&pages=43)

27. Orme JJ, Jazieh KA, Xie T, Harrington S, Liu X, Ball M, et al. ADAM10 and ADAM17 cleave PD-L1 to mediate PD-(L)1 inhibitor resistance. *Oncoimmunology.* (2020) 9: 1744980. doi: 10. 1080/2162402X. 2020. 1744980

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/32363112) | [CrossRef Full Text](https://doi.org/10.1080/2162402X.2020.1744980) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=JJ.+Orme&author=KA.+Jazieh&author=T.+Xie&author=S.+Harrington&author=X.+Liu&author=M.+Ball+&publication_year=2020&title=ADAM10+and+ADAM17+cleave+PD-L1+to+mediate+PD-(L)1+inhibitor+resistance&journal=Oncoimmunology.&volume=9&pages=1744980)

28. Madoux F, Dreymuller D, Pettiloud JP, Santos R, Becker-Pauly C, Ludwig A, et al. Discovery of an enzyme and substrate selective inhibitor of ADAM10 using an exosite-binding glycosylated substrate. *Sci Rep.* (2016) 6: 11. doi: 10. 1038/s41598-016-0013-4

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/28442704) | [CrossRef Full Text](https://doi.org/10.1038/s41598-016-0013-4) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=F.+Madoux&author=D.+Dreymuller&author=JP.+Pettiloud&author=R.+Santos&author=C.+Becker-Pauly&author=A.+Ludwig+&publication_year=2016&title=Discovery+of+an+enzyme+and+substrate+selective+inhibitor+of+ADAM10+using+an+exosite-binding+glycosylated+substrate&journal=Sci+Rep.&volume=6&pages=11)

29. Saha N, Robev D, Himanen JP, Nikolov DB. ADAM proteases: emerging role and targeting of the non-catalytic domains. *Cancer Lett.* (2019) 467: 50–7. doi: 10. 1016/j. canlet. 2019. 10. 003

[PubMed Abstract](https://pubmed.ncbi.nlm.nih.gov/31593799) | [CrossRef Full Text](https://doi.org/10.1016/j.canlet.2019.10.003) | [Google Scholar](http://scholar.google.com/scholar_lookup?author=N.+Saha&author=D.+Robev&author=JP.+Himanen&author=DB.+Nikolov+&publication_year=2019&title=ADAM+proteases%3A+emerging+role+and+targeting+of+the+non-catalytic+domains&journal=Cancer+Lett.&volume=467&pages=50-7)