

# Oligonucleotide-based PROTACs to Degrade RNA- and DNA-Binding Proteins

Céline N. Weller and Jonathan Hall\*

**Abstract:** Proteolysis targeting chimeras (PROTACs) are heterobifunctional molecules that sequester the endogenous protein degradation machinery of cells to induce degradation of targeted proteins. By bringing a target protein and a ubiquitin E3 ligase into close proximity, ubiquitin monomers can be transferred onto surface lysines of the protein, which is subsequently degraded by the proteasome. The functions of RNA- and DNA-binding proteins have been especially hard to modulate with small molecules. However, oligonucleotides that bind RNA- or DNA-binding proteins can be turned into oligonucleotide-based PROTACs to direct ubiquitination and degradation of these proteins. Here we summarize the current state of the field of oligonucleotide-based PROTACs that target RNA- or DNA-binding proteins.

**Keywords:** DNA-binding proteins · Oligonucleotide-based PROTACs · RNA-binding proteins · RNA-PROTAC · Targeted protein degradation



**Céline Noémie Weller** is a doctoral student in the group of Prof. Jonathan Hall at ETH Zürich. She works on RNA-PROTACs to develop tools to induce ubiquitination and degradation of proteins implicated in neurodegenerative diseases.



**Jonathan Hall** received his PhD at Imperial College in London in 1988. He did a post-doc with J.-M. Lehn in Strasbourg and with Y. Kishi in Cambridge (USA). He joined Novartis in Basel in 1992. In 2007 he moved to the ETH Zurich as a Professor of Pharmaceutical Chemistry. A principal goal of his group at the ETH is to help bring RNA as a drug and a target into mainstream pharmaceutical research.

## 1. Oligonucleotide-based PROTACs

Proteolysis targeting chimeras (PROTACs) are heterobifunctional molecules that sequester the endogenous ubiquitin-proteasome system (UPS) to induce degradation of target proteins of interest (POI) (Fig. 1A).<sup>[1]</sup> Three moieties are assembled to form a PROTAC: a ‘warhead’ that binds tightly and selectively to the POI, a ligand fragment that sequesters an appropriate E3 ubiquitin ligase and a linker connecting the two groups.<sup>[2]</sup> The POI and the E3 ubiquitin ligase form a ternary complex with the PROTAC, which results in the transfer of ubiquitin moieties onto proximal surface lysine residues of the POI. The ubiquitinated POI is thereafter recognized by the proteasome and subsequently degraded, while the PROTAC is recycled in a formal catalytic cycle.<sup>[3]</sup> This new type of pharmacology offers a means to selectively degrade (inhibit) pathologically relevant proteins that cannot be addressed by conventional approaches requiring small-ligand-compatible binding sites (*e.g.* receptors and enzymes). PROTACs and their variants also serve as a means to endow weakly active conven-

tional small molecule drugs with additional potency<sup>[4]</sup> and may also be exploited as new tools in chemical biology. Recently, alternative classes of warheads to conventional small molecule PROTACs have emerged, based on peptides or oligonucleotides.<sup>[5]</sup> Our laboratory introduced the first RNA-PROTAC in 2020;<sup>[6]</sup> an oligonucleotide conjugate that binds to the RNA-binding protein (RBP) and stem cell factor Lin28 *via* a short, structurally modified oligo-ribonucleotide that is *iso*-sequential to the Lin28A and Lin28B RNA-binding element (Fig. 1B). Since then, several oligonucleotide-based PROTACs targeting RNA- or DNA-binding proteins have emerged. In this manuscript we review recent developments in oligonucleotide-based PROTACs.

### 1.1 Oligonucleotide-based PROTACs Targeting RNA-Binding Proteins

RBPs regulate a myriad of cellular functions.<sup>[7]</sup> Furthermore, the aberrant functions of RBPs have been linked to commonly occurring cancers and neurodegenerative diseases, as well as to rare diseases.<sup>[8]</sup> Notably, except for a few natural product structures, RBP function is particularly difficult to inhibit through the rational design of small molecule ligands. This is because RBPs lack a ‘ligandable’ binding pocket that is functional and suitable for the binding of conventional small-molecule drug structures, *i.e.* low molecular weight ligands with moderate to high hydrophobicity. However, RBPs do bind cellular RNAs with high affinity and selectivity, often using multiple RNA-binding domains to contact ribonucleotides with a conglomerate of electrostatic, H-bonding and hydrophobic interactions with all parts of the ribose and the nucleobases.

We designed the first RNA-PROTAC to target the RBP Lin28A and its paralog Lin28B using a phosphorothioated (PS) 2′-O-methoxyethyl (MOE)-modified version of 5′ AGGUAG, the conserved RNA binding consensus sequence for the zinc finger domain of Lin28A/B<sup>[6,9]</sup> (Table 1; Entry 1). Lin28 proteins regulate the biogenesis of microRNAs and the translation of messenger RNAs (mRNAs) using their zinc finger and cold shock domains.<sup>[10]</sup> The use of a structurally modified RNA as the targeting ligand is warranted since native RNAs are readily degraded by ubiquitous nucleases *in vivo*. This introduces a constraint in ligand design since bulky RNA modifications on one hand protect against nuclease degradation, but on the other hand risk to attenuate binding affinity to the target POI.

\*Correspondence: Prof. J. Hall, E-mail: jonathan.hall@pharma.ethz.ch  
Department of Chemistry and Applied Biosciences, ETH Zürich, CH-8093 Zürich.

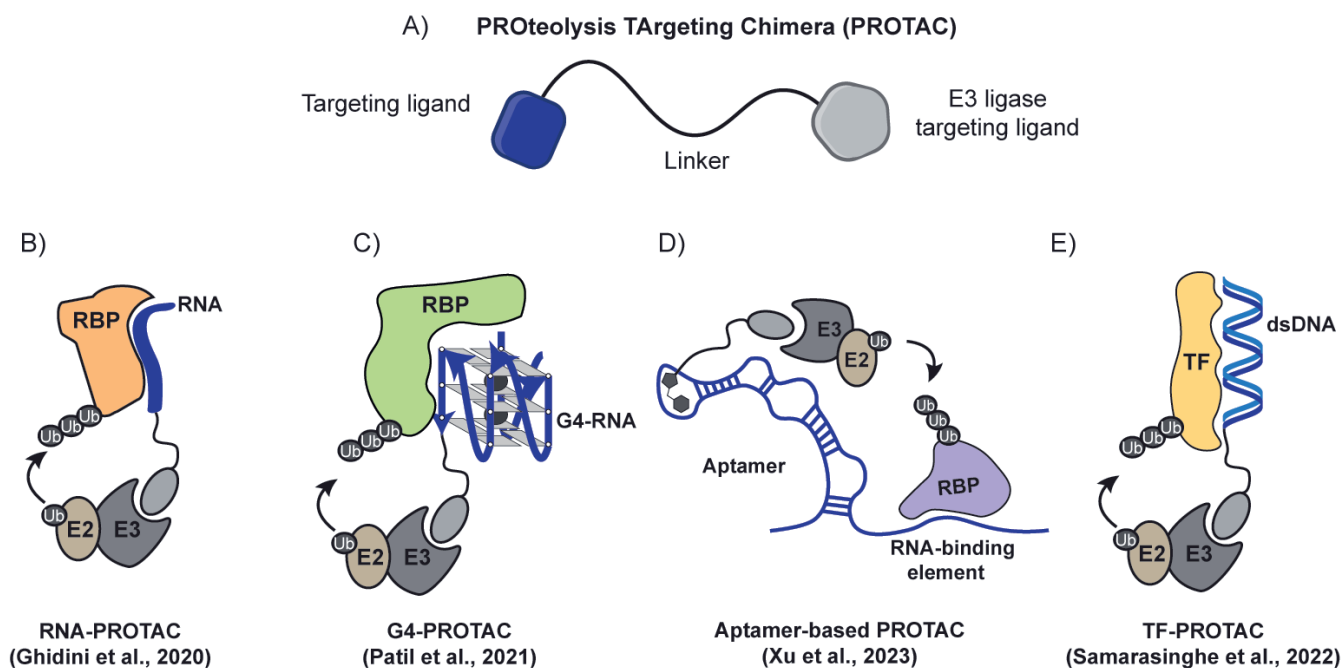


Fig. 1. Oligonucleotide PROTACs. A) The classical composition of a PROTAC ligand comprising the warhead, a linker and an E3 ligase recruiting molecule. B) RNA-PROTACs induce degradation of RNA-binding proteins (RBP) using a short, modified oligonucleotide conjugated to an E3 ligase recruiting moiety. C) G-Quadruplex-based PROTACs use a G4 conjugated to an E3 ligase recruiting molecule to degrade helicases. D) Aptamer-based PROTACs encode an aptamer to bind a small molecule fused to an E3 recruiting moiety and an RNA-binding element (RBE) of target RNA-binding proteins (RBP). When the small molecule binding the aptamer and the E3 ligase is added, the RNA-binding protein is degraded. E) Oligonucleotide-based PROTACs comprised of double stranded DNA conjugated to an E3 ligase recruiting molecule to degrade transcription factors (TF).

The MOE-PS heptanucleotide was conjugated to a von Hippel-Lindau (VHL)-recruiting peptide, or VH032. The short VHL peptide is commonly used in PROTACs<sup>[11]</sup> since it sequesters a ubiquitously expressed E3 ligase that activates proteasomal degradation.<sup>[12]</sup> VH032 is a small molecule ligand that similarly sequesters the VHL E3.<sup>[13]</sup> Upon RNA-PROTAC treatment, proteasome-dependent degradation of the cytosolic isoform Lin28A was observed. Using an identical approach, an RNA PROTAC was established against RBFOX1, in this case targeting the RNA-recognition motif (RRM) domain of this alternative splice factor.<sup>[6]</sup> In 2024, a similar RNA-PROTAC targeting Lin28 proteins was described by the Xu group. In this example, a longer stretch of PS RNA comprising the zinc finger RNA binding consensus was used, conjugated to a small molecule ligand for the E3 ligase Cereblon (CRBN) to degrade Lin28 (Table 1; Entry 2). When complexed in a lipid nanoparticle, this reagent decreased growth of tumors in mice after intratumoral injection.<sup>[14]</sup>

While these first-generation RNA PROTACs used single stranded short RNAs with a conserved binding sequence as a targeting warhead for the RBP, two separate groups have developed oligonucleotide-based PROTACs that use a DNA G-quadruplex (G4) tertiary structure as the targeting moiety to address RBPs with helicase function (Fig. 1C). The first example describes a G4-PROTAC that binds and degrades RHAU, an RNA helicase encoded by the *DH36* gene, that is highly expressed in neurons of patients suffering from Corf72-linked amyotrophic lateral sclerosis (ALS).<sup>[15]</sup> The G4-PROTAC was constructed using an all-parallel TT(GGGT)<sup>4</sup> DNA quadruplex stabilized against nuclease degradation by a terminal PS linkage (Table 1; Entry 3). When delivered into HeLa and K562 cells, the G4-PROTAC induced degradation of RHAU.<sup>[16]</sup> The second example of a G4-based PROTAC was designed to target fragile-X messenger RNA ribonucleoprotein (FMRP), a protein expressed in the brain, which is essential for cognitive development.<sup>[17]</sup> In this case, a G4-RNA quadruplex bearing a five base-pair stem was conjugated *via* a

peptide linker to the VHL recruiting peptide (Table 1; Entry 4). Experiments performed *in vitro*, revealed a proteasome-dependent depletion of FMRP.<sup>[18]</sup>

An alternative innovative approach to induce the degradation of RBPs utilizes an aptamer-based PROTAC. Here, a plasmid was constructed that expresses the RNA-binding element of Lin28 or RBFOX fused to the 3'-end of the 'broccoli' aptamer that binds selectively to the small molecule 3,5-difluoro-4-hydroxybenzylidene imidazolinone (DFHBI). DFHBI is in turn conjugated through a short linker to pomalidomide, which recruits the E3 ligase CRBN. The small molecule is easily delivered into HEK293T cells expressing the aptamer and induces the ternary complex that degrades protein bound by the RNA binding domain (Fig. 1D). The advantage of this system is that by changing the sequence of the RNA binding element in the aptamer, different RBPs can be degraded (Table 1; Entry 5). The system was validated by showing degradation of Lin28, RBFOX, p50 and E2F1 proteins.<sup>[19]</sup>

## 1.2 Oligonucleotide-based PROTACs Targeting Transcription Factors

Oligonucleotides have also been employed to target DNA-binding proteins, for example transcription factors. Like RBPs, transcription factors are attractive drug targets, particularly for their roles in selected cancers.<sup>[20]</sup> They are also considered to be undruggable with conventional small-molecule drugs. Hence, transcription factor targeting chimeric molecules (TRAFTACs) were introduced. The first reported TRAFTAC employed a short double-stranded DNA (dsDNA) fused to a dCas9-RNA (Table 1; Entry 6). The DNA/RNA construct binds to a dCas9-HT7 fusion protein forming a ternary complex with the transcription factor of interest. Addition of a HaloPROTAC that sequesters HT7 and VHL, results in the ubiquitination and subsequent degradation of the transcription factor. With this system, the transcription factors brachyury, a key factor in embryogenic development, and NF- $\kappa$ B, a promoter of cell survival, were successfully targeted

Table 1. Oligonucleotide PROTACs and their properties.

Entry	Target Protein	Sequence of the Oligonucleotide (5' to 3')	Chemistry of the Oligonucleotide	E3 ligase	Ref.
1	Lin28, RBFOX	AGGAGAU (Lin28), UGCAUGU (RBFOX)	2'methoxyethyl, PS <sup>a</sup> backbone	VHL <sup>b</sup>	[16]
2	Lin28	Let7 precursor	RNA, PS <sup>a</sup> backbone	CRBN <sup>c</sup>	[14]
3	RHAU	TT(GGGT) <sup>4</sup>	DNA, 1 PS <sup>a</sup> linkage	CRBN <sup>c</sup> and VHL <sup>b</sup>	[16]
4	FMRP	GCUGCGGUGUGGAAGGAGUGGCUGGGUU GCGCAGCG	RNA	VHL <sup>b</sup>	[18]
5	Lin28, RBFOX, p50 and E2F1	AGGAGAU (Lin28), UGCAUGU (RBFOX), GATCTTGAAACTGTTTAAAGTTGGCCGA TCTT (p50), GGGAGAGCGGAAGCGTGCTGGGCCATGG AGTCGATGTGATAAGTAGGACGGAGGTGG TCGATACATAACCCAGAGGTCGATGGATC CCCCC (E2F)	plasmid	CRBN <sup>c</sup>	[19]
6	Brachyury, c-myc	AATTCACACCTAGGTGTGAAATT (brachyury), GTGCACCGTTGGTGCAC (c-myc)	DNA, PS <sup>a</sup> backbone	VHL <sup>2</sup>	[21, 22]
7	LEF1, ERG	TACAAAGATCAAAGGGTT (LEF1), ACGGACCGGAAATCCGGTT (ERG)	DNA duplex	CRBN <sup>c</sup> and VHL <sup>b</sup>	[23a]
8	NF-kB, E2F	TGGGGACTTTCCAGTTTCTGGAAAGTCCCCA (NF-kB), CTAGATTTCCCGCG (E2F)	DNA hairpin	VHL <sup>b</sup>	[23b]
9	c-myc	GAGTAGCACGTGCTAC GTAGCACGTGCTACTC	DNA duplex	VHL <sup>b</sup>	[23c]
10	STAT3	CATTTCCCGTAAATC GATTACGGGAAATG	DNA duplex	CRBN <sup>c</sup>	[24]
11	STAT3	CATTTCCCGTAAATC -linker- GATTACGGGAAATG	DNA hairpin, PS <sup>a</sup> linkages	CRBN <sup>c</sup>	[25]
12	EP $\alpha$	GTCAGGTCACAGTGACCTGAT ATCAGGTCAGTATGCCTGAC	DNA duplex	IAP <sup>d</sup>	[26]
13	ER $\alpha$	GTCAGGTCACAGTGACCTGAT ATCAGGTCAGTATGCCTGAC	DNA hairpin, PS <sup>a</sup> backbone	IAP <sup>d</sup>	[27]
14	ER $\alpha$	GTCAGGTCACAGTGACCTGAT ATCAGGTCAGTATGCCTGAC	DNA hairpin, PS <sup>a</sup> backbone, DNA/RNA heteroduplex	IAP <sup>d</sup>	[28]
15	ER $\alpha$	CCCGCATGGTTGCGGAGCAGGAGTATAA CACTACCATTG	DNA	VHL <sup>b</sup>	[29]

<sup>a</sup>Phosphorothioate, <sup>b</sup>Von Hippel-Lindau ubiquitin E3 ligase, <sup>c</sup>Cereblon ubiquitin E3 ligase, <sup>d</sup>Inhibitor of Apoptosis protein

for degradation in cells.<sup>[21]</sup> The system for targeting transcription factors was subsequently simplified and optimized by the same research group to OligoTRAFTACs, constructs where a PS DNA duplex is directly conjugated to a small molecule ligand of VHL (Fig. 1E). OligoTRAFTACs induce degradation of brachyury and c-myc in cells and in zebrafish.<sup>[22]</sup> Along with the report of the first TRAFTAC, several research groups designed transcription

factor-targeting oligonucleotide-based PROTACs,<sup>[23]</sup> which were given a variety of different names.

The O'PROTAC is a minimal-length oligonucleotide PROTAC that consists of double-stranded DNA coupled to VH032 (Table 1; Entry 7).<sup>[23a]</sup> Transcription factors LEF1 and ERG are both cancer-related proteins that have been targeted for degradation by O'PROTACs in cells. These reagents have also been used in

mouse xenograft models of cancer, whereby the O<sup>o</sup>PROTAC was condensed with polyethyleneimine and injected directly into the tumors, leading to a significant reduction in tumor volume. Similar reports described by other groups that use double-stranded DNA as the targeting warhead include a PROTAC (TF-PROTAC) that binds and degrades E2F, causing decreased cell proliferation in HeLa cells (Table 1; Entry 8);<sup>[23b]</sup> a c-myc targeting PROTAC designed using the X-ray structure of the c-myc-MAX complex with DNA. The DNA-duplex was conjugated to VH032. Treatment with this reagent decreases the cell viability of multiple hepatocellular cancer cell lines and reduces the tumor volume in xenograft mouse models of cancer (Table 1; Entry 9).<sup>[23c]</sup> Similarly, Shih *et al.* described a DNA duplex linked to pomalidomide which triggered proteasome-dependent degradation of STAT3 in a lung cancer cell line (Table 1; Entry 10).<sup>[24]</sup>

In the same year, Hall *et al.* reported an Oligo-PROTAC targeting STAT3 using a hairpin PS DNA fused to thalidomide (Table 1; Entry 11). Interestingly, the DNA hairpin carried a CpG-motif to facilitate uptake of the Oligo-PROTAC into TLR9-expressing immune cells within the tumor microenvironment. Intratumoral injection of the Oligo-PROTAC in tumor-xenograft-bearing mice led to a significant reduction in tumor volume compared to only the decoy STAT3 binding DNA or vehicle controls.<sup>[25]</sup>

Similarly, but distinct from PROTACs, IAP-based degraders allow the covalent crosslinking of the protein of interest with the E3 ubiquitin ligase cIAP1. cIAP1 autoubiquitination together with the fused protein of interest is triggered, followed by degradation of the complex through the proteasome.<sup>[31]</sup> The first IAP-based degrader contained a DNA duplex designed using the X-ray structure of the estrogen receptor alpha (ER $\alpha$ ) with DNA (Table 1; Entry 12). Treatment of the breast cancer cell line MCF-7 with the IAP-based degrader, resulted in proteasome-dependent depletion of ER $\alpha$ .<sup>[26]</sup> The same group further optimized the ER $\alpha$ -degrader with a second-generation targeting ligand that employed a PS DNA hairpin for increased nuclease stability (Table 1; Entry 13).<sup>[27]</sup> Finally, to address the well known challenges of cellular delivery associated with oligonucleotide therapeutics, a cell-penetrating peptide (CPP) and a heteroduplex oligonucleotide (HDO) were conjugated to the ER $\alpha$ -degrader (Table 1; Entry 14); the CPP augments cellular uptake, and is released from the ER $\alpha$ -degrader by cleavage with RNase H in cells.<sup>[28]</sup> An alternative means to target ER $\alpha$  degradation was achieved by fusing an ER $\alpha$ -binding DNA aptamer to VH032 (Table 1; Entry 15). Aptamers with high affinity for proteins can be generated by systematic evolution of ligands by exponential enrichment (SELEX).<sup>[32]</sup> The aptamer-based PROTAC induced degradation of ER $\alpha$  in MCF-7 cells and decreased estrogen-dependent transcriptional activity of ER $\alpha$ .<sup>[29]</sup> Aptamers have been incorporated into PROTACs targeting DNA binding proteins or even added to PROTACs to increase their uptake into specific cell types.<sup>[33,34]</sup>

### 3. Conclusions

The emergence of oligonucleotide-based PROTACs from the first RNA-PROTAC<sup>[6]</sup> has opened a new avenue to the targeted rational degradation of RNA- and DNA-binding proteins. A wide variety of oligonucleotides have been leveraged to induce degradation of proteins of interest. These PROTACs have been effective *in vitro* and *in vivo* at degrading RNA- or DNA-binding proteins implicated in cancer and other diseases.

### Acknowledgements

This work was partly supported by the NCCR RNA and Disease of the SNSF (Grant number: 51NF40-205601 to J.H.)

Received: January 31, 2025

- [1] K. Li, C. M. Crews, *Chem. Soc. Rev.* **2022**, *51*, 5214, <https://doi.org/10.1039/d2cs00193d>.
- [2] K. M. Sakamoto, K. B. Kim, A. Kumagai, F. Mercurio, C. M. Crews, R. J. Deshaies, *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98*, 8554, <https://doi.org/10.1073/pnas.141230798>.
- [3] D. A. Nalawansa, C. M. Crews, *Cell. Chem. Biol.* **2020**, *27*, 998, <https://doi.org/10.1016/j.chembiol.2020.07.020>.
- [4] M. Bekes, D. R. Langley, C. M. Crews, *Nat. Rev. Drug Discovery* **2022**, *21*, 181, <https://doi.org/10.1038/s41573-021-00371-6>.
- [5] Z. Hu, C. M. Crews, *Chembiochem* **2022**, *23*, e202100270, <https://doi.org/10.1002/cbic.202100270>.
- [6] A. Ghidini, A. Clery, F. Halloy, F. H. T. Allain, J. Hall, *Angew. Chem. Int. Ed.* **2020**, *60*, 3163, <https://doi.org/10.1002/anie.202012330>.
- [7] W. H. Hudson, E. A. Ortlund, *Nat. Rev. Mol. Cell Biol.* **2014**, *15*, 749, <https://doi.org/10.1038/nrm3884>.
- [8] S. Kelaini, C. Chan, V. A. Cornelius, A. Margariti, *Biology* **2021**, *10*, 366, <https://doi.org/10.3390/biology10050366>.
- [9] F. E. Loughlin, L. F. Gebert, H. Towbin, A. Brunschweiler, J. Hall, F. H. Allain, *Nat. Struct. Mol. Biol.* **2011**, *19*, 84, <https://doi.org/10.1038/nsmb.2202>.
- [10] E. G. Moss, L. Tang, *Dev. Biol.* **2003**, *258*, 432, [https://doi.org/10.1016/s0012-1606\(03\)00126-x](https://doi.org/10.1016/s0012-1606(03)00126-x).
- [11] I. Sosic, A. Bricelj, C. Steinebach, *Chem. Soc. Rev.* **2022**, *51*, 3487, <https://doi.org/10.1039/d2cs00148a>.
- [12] J. S. Schneekloth, Jr., F. N. Fonseca, M. Koldobskiy, A. Mandal, R. Deshaies, K. Sakamoto, C. M. Crews, *J. Am. Chem. Soc.* **2004**, *126*, 3748, <https://doi.org/10.1021/ja039025z>.
- [13] C. Galdeano, M. S. Gadd, P. Soares, S. Scaffidi, I. Van Molle, I. Birced, S. Hewitt, D. M. Dias, A. Ciulli, *J. Med. Chem.* **2014**, *57*, 8657, <https://doi.org/10.1021/jm5011258>.
- [14] J. Xu, X. Zhao, X. Liang, D. Guo, J. Wang, Q. Wang, X. Tang, *Sci. Adv.* **2024**, *10*, eadp0334, <https://doi.org/10.1126/sciadv.adp0334>.
- [15] H. Liu, Y. N. Lu, T. Paul, G. Periz, M. T. Banco, A. R. Ferre-D'Amare, J. D. Rothstein, L. R. Hayes, S. Myong, J. Wang, *J. Am. Chem. Soc.* **2021**, *143*, 7368, <https://doi.org/10.1021/jacs.1c00131>.
- [16] K. M. Patil, D. Chin, H. L. Seah, Q. Shi, K. W. Lim, A. T. Phan, *Chem. Commun.* **2021**, *57*, 12816, <https://doi.org/10.1039/d1cc05025g>.
- [17] L. K. Myrick, M. Nakamoto-Kinoshita, N. M. Lindor, S. Kirmani, X. Cheng, S. T. Warren, *Eur. J. Hum. Genet.* **2014**, *22*, 1185, <https://doi.org/10.1038/ejhg.2013.311>.
- [18] R. Peng, Q. Huang, L. Wang, G. Qiao, X. Huang, J. Jiang, X. Chu, *Angew. Chem. Int. Ed.* **2024**, *63*, e202402715, <https://doi.org/10.1002/anie.202402715>.
- [19] Y. Xu, Y. Yuan, D. Q. Fu, Y. Fu, S. Zhou, W. T. Yang, X. Y. Wang, G. X. Li, J. Dong, F. Du, X. Huang, Q. W. Wang, Z. Tang, *Bioorg. Med. Chem.* **2023**, *86*, 117299, <https://doi.org/10.1016/j.bmc.2023.117299>.
- [20] M. Lambert, S. Jambon, S. Depauw, M. H. David-Cordonnier, *Molecules* **2018**, *23*, <https://doi.org/10.3390/molecules23061479>.
- [21] K. T. G. Samarasinghe, S. Jaime-Figueroa, M. Burgess, D. A. Nalawansa, K. Dai, Z. Hu, A. Bebenek, S. A. Holley, C. M. Crews, *Cell Chem. Biol.* **2021**, *28*, 648, <https://doi.org/10.1016/j.chembiol.2021.03.011>.
- [22] K. T. G. Samarasinghe, E. An, M. A. Genuth, L. Chu, S. A. Holley, C. M. Crews, *RSC Chem. Biol.* **2022**, *3*, 1144, <https://doi.org/10.1039/d2cb00138a>.
- [23] a) J. Shao, Y. Yan, D. Ding, D. Wang, Y. He, Y. Pan, W. Yan, A. Kharbanda, H. Y. Li, H. Huang, *Adv. Sci.* **2021**, *8*, e2102555, <https://doi.org/10.1002/advs.202102555>; b) J. Liu, H. Chen, H. U. Kaniskan, L. Xie, X. Chen, J. Jin, W. Wei, *J. Am. Chem. Soc.* **2021**, *143*, 8902, <https://doi.org/10.1021/jacs.1c03852>; c) M. Ai, H. Ma, J. He, F. Xu, Y. Ming, Z. Ye, Q. Zheng, D. Luo, K. Yang, J. Li, C. Nie, W. Pu, Y. Peng, *Eur. J. Med. Chem.* **2024**, *280*, 116978, <https://doi.org/10.1016/j.ejmech.2024.116978>.
- [24] P. C. Shih, M. Naganuma, G. Tsuji, Y. Demizu, M. Naito, *Bioorg. Med. Chem.* **2023**, *95*, 117507, <https://doi.org/10.1016/j.bmc.2023.117507>.
- [25] J. Hall, Z. Zhang, S. Bhattacharya, D. Wang, M. Alcantara, Y. Liang, P. Swiderski, S. Forman, L. Kwak, N. Vaidehi, M. Kortylewski, *Mol. Ther. Nucleic Acids* **2024**, *35*, 102137, <https://doi.org/10.1016/j.omtn.2024.102137>.
- [26] M. Naganuma, N. Ohoka, G. Tsuji, H. Tsujimura, K. Matsuno, T. Inoue, M. Naito, Y. Demizu, *ACS Med. Chem. Lett.* **2022**, *13*, 134, <https://doi.org/10.1021/acsmchemlett.1c00629>.
- [27] M. Naganuma, N. Ohoka, G. Tsuji, T. Inoue, M. Naito, Y. Demizu, *Bioconjugate Chem.* **2023**, *34*, 1780, <https://doi.org/10.1021/acs.bioconjchem.3c00332>.
- [28] M. Naganuma, N. Ohoka, M. Hirano, D. Watanabe, G. Tsuji, T. Inoue, Y. Demizu, *RSC Med. Chem.* **2024**, *15*, 3695, <https://doi.org/10.1039/d4md00546e>.
- [29] H. Tsujimura, M. Naganuma, N. Ohoka, T. Inoue, M. Naito, G. Tsuji, Y. Demizu, *ACS Med. Chem. Lett.* **2023**, *14*, 827, <https://doi.org/10.1021/acsmchemlett.3c00126>.
- [30] S. Li, T. Zeng, Z. Wu, J. Huang, X. Cao, Y. Liu, S. Bai, Q. Chen, C. Li, C. Lu, H. Yang, *J. Am. Chem. Soc.* **2025**, *147*, 2168, <https://doi.org/10.1021/jacs.4c16438>.

- [31] K. Okuhira, Y. Demizu, T. Hattori, N. Ohoka, N. Shibata, T. Nishimaki-Mogami, H. Okuda, M. Kurihara, M. Naito, *Cancer Sci.* **2013**, *104*, 1492, <https://doi.org/10.1111/cas.12272>.
- [32] a) L. Gold, *J. Mol. Evol.* **2015**, *81*, 140, <https://doi.org/10.1007/s00239-015-9705-9>; b) D. Irvine, C. Tuerk, L. Gold, *J. Mol. Biol.* **1991**, *222*, 739, [https://doi.org/10.1016/0022-2836\(91\)90509-5](https://doi.org/10.1016/0022-2836(91)90509-5).
- [33] X. Li, Z. Zhang, F. Gao, Y. Ma, D. Wei, Z. Lu, S. Chen, M. Wang, Y. Wang, K. Xu, R. Wang, F. Xu, J. Y. Chen, C. Zhu, Z. Li, H. Yu, X. Guan, *J. Am. Chem. Soc.* **2023**, *145*, 9334, <https://doi.org/10.1021/jacs.3c02619>.
- [34] S. He, F. Gao, J. Ma, H. Ma, G. Dong, C. Sheng, *Angew. Chem. Int. Ed.* **2021**, *60*, 23299, <https://doi.org/10.1002/anie.202107347>.

#### License and Terms



This is an Open Access article under the terms of the Creative Commons Attribution License CC BY 4.0. The material may not be used for commercial purposes.

The license is subject to the CHIMIA terms and conditions: (<https://chimia.ch/chimia/about>).

The definitive version of this article is the electronic one that can be found at <https://doi.org/10.2533/chimia.2025.167>