

Research Article

NR4A3 Fusion-Junction Antisense Gapmers for Extraskelatal Myxoid Chondrosarcoma: Reagents, Test Articles and a Pre-Registrable Knockdown Experiment

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Extraskelatal myxoid chondrosarcoma (EMC) is an ultra-rare sarcoma usually defined by an in-frame *NR4A3* fusion, its junction in no normal transcript. An antisense gapmer could in principle cleave it, sparing the parents; none is reported. The work is computational — an industry off-target framework's in-silico step; every sequence is a research reagent not for administration. It names what a laboratory needs: two reagents at the most-reported breakpoints — 5'-GGGCATATCATCAAAC-3' at *EWSR1* exon 12 and 5'-GGGCATATCTTGTGTG-3' at *TAF15* exon 6, both to *NR4A3* exon 3, longest wild-type parent gap duplexes eight and nine base pairs — two screened controls, a pre-registrable selectivity threshold. Both come from 190 junction-spanning 16-mers across 38 in-frame junctions; 87 let a mature wild-type parent pair their whole catalytic gap over ten or more contiguous base pairs, 61 against wild-type *NR4A3*. Ten is a convention, not a measurement: exon-terminus chimeras meet the same screen at 40.6% against the panel's 45.8%. Five test articles are named; the two fusion-positive EMC cell models are reported at an *NR4A3* exon-2 acceptor, not this panel's. Designability is not the constraint; discrimination from the parents is. That liability is invisible to a conventional off-target search and must be screened directly before synthesis.

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Introduction

EMC is defined in the large majority of cases by an in-frame fusion of *EWSR1* to *NR4A3*^[1], with *TAF15* a substantial minority and *TCF12* and *TFG* rare^[2]. The disease responds poorly to conventional cytotoxic chemotherapy^[3], though responses do occur^[4], and a tyrosine-kinase inhibitor trialled in it gave disease control more often than response — a reading composed from the review's response categories^[3] rather than from a figure stated in the trial report^[5].

The fusion junction is the one feature of an EMC tumour that exists at the RNA level and in no normal cell. An antisense gapmer tiled across it recruits RNase-H1 to cleave the transcript it pairs, at the six-nucleotide DNA gap at the centre of a 5-6-5 architecture. Junction-directed nucleic-acid agents are a thirty-five-year lineage, reported against at least six fusion oncogenes: two as antisense oligonucleotides, the rest as RNA-interference agents, one of those from a lentiviral vector rather than an administered oligonucleotide^{[6][7][8][9][10][11]}. No such design is reported for any *NR4A3* fusion in the literature retrieved here.

What a junction design must survive follows from its construction. Both halves are parent-gene sequence, so each parent matches roughly half the oligonucleotide — far outside the mismatch budget of a conventional off-target search, which therefore never returns a parent as a near-match. That parent liability is the one this work screens for directly, and the case for screening it is structural rather than statistical: it is invisible to the instrument a designer would ordinarily use, at any threshold that instrument is normally run at, whatever cut the direct screen then adopts. RNase-H1 does not require the whole duplex, only that the gap be paired — a premise adopted here rather than established, and one whose length requirement is stated in a different unit from the criterion this paper screens on. The requirement is reported as a DNA gap of at least six nucleotides, with seven to ten the working range; the screen below counts a liability only at ten contiguous base pairs of duplex through that gap, a length of hybrid rather than a count of gap nucleotides. Whether a wild-type parent pairs the catalytic gap contiguously is therefore a separate question from overall similarity. That direction is the one an industry working group's 2025 off-target recommendations report: off-target effects are seen more often where an oligonucleotide's mismatches fall in its wings than where they fall in its central gap, on which reading a flanking mismatch is suggested as the more important one to avoid^[12]. Those recommendations set five steps: in-silico identification with transcriptomics, a focus on cell types showing activity, in-vitro verification and margin assessment, risk assessment of what is confirmed, and management of what

remains. This work performs the in-silico half of the first step and stops there; the margin measurement of the third is what the Discussion specifies, against the wild-type parent the panel screen below identifies as the liability.

Materials and Methods

All analyses are computational and use public data; no laboratory work was performed. Full parameters, the complete bounds on each claim and the per-design tables are in the archived deposit named under Data availability.

Canonical transcripts for the five partner genes and for *NR4A3* were obtained from Ensembl^[13]. Junction-spanning 16-mer gapmers were tiled in a 5-6-5 β -D-oxy-locked nucleic acid (LNA)/DNA/LNA geometry^[14], one design per register at which the breakpoint falls inside the six-nucleotide DNA gap, which admits five per junction. That gap is the shortest length the cited source credits rather than its preferred one, and six is used because the genome-wide arm is not available above a 16-mer. A design's gap-level margin is the count of junction-unique bases inside the gap on the shorter side of the breakpoint.

Five specificity screens were applied: an alignment screen against human RefSeq RNA, classifying each near-match by whether the catalytic gap is paired; an exhaustive transcript scan complete for substitutions within a one-mismatch budget; a screen of the parents' unspliced sequence; a mature-parent screen recording the longest contiguous duplex any of six wild-type parent transcripts forms through the catalytic gap; and a genome-wide screen over every position of GRCh38, mitochondrial sequence included. Between them they cover mature transcript, unspliced precursor, exon-exon junction, non-coding and mitochondrial sequence — the search scope the 2025 recommendations ask for^[12]. A near-match is a transcript window pairing a design at 14 or more of its 16 positions. Each alignment was re-scored on the nearest-neighbour stability of its longest contiguous paired run — the energy-based second stage those recommendations prescribe — and only separations are reported. A design is liable where a wild-type parent pairs its whole catalytic gap over a contiguous run of ten base pairs or more, ten being adopted rather than measured. Null ensembles were built as scrambles of each design and as chimeras joining the same two parent transcripts at real exon termini, screened identically. Melting temperatures are nearest-neighbour values for an unmodified DNA:RNA hybrid at 250 nM strand^[15]. That is not a locked phosphorothioate oligonucleotide, so no absolute melting point is reported. Only the

fusion-versus-parent separation is, and as a floor: the fusion duplex pairs all ten locked residues where each parent pairs five.

Results

The reagents

The two reagents named for synthesis are the best available designs at the two junctions with a published exon-resolved breakpoint and the highest reported prevalence: 5'-GGGCATATCATCAAAC-3' at *EWSR1* exon 12 joined to *NR4A3* exon 3, and 5'-GGGCATATCTTGTGTG-3' at *TAF15* exon 6 joined to *NR4A3* exon 3 (Table 1). Exon numbers throughout are transcript exon indices counted from the transcript 5' end, including non-coding exons; an acceptor exon number read under the coding-exon convention instead selects a different reagent. Both hold the panel's top gap-level margin of three: three junction-unique bases inside the catalytic gap on the shorter side of the breakpoint, and neither pairs a wild-type parent through the gap at the ten-base-pair criterion Methods sets.

Both sit close to it. The *EWSR1* reagent's longest wild-type parent duplex through the whole gap is eight base pairs and the *TAF15* reagent's is nine, both against wild-type *TFG*. The cut therefore decides how they read: at eight both fall inside the class this work marks as not to be ordered, at nine the *TAF15* reagent alone does, and only at ten does neither. Both also pair a wild-type parent through part of the gap at the *NR4A3* exon-2/exon-3 seam their acceptor halves share, neither in full; those partial duplexes are not counted here and have not been measured. Consecutive registers of one seam differ by a single-base slide and can carry opposite verdicts, and one slide from a named reagent is condemned: 5'-AGGGCATATCTTGTGTG-3' is one slide from the *TAF15* reagent and pairs 11 base pairs of wild-type *NR4A3* through its whole catalytic gap. Neither may be substituted for the other.

Predicted transcriptome load separates the two: 123 gap-paired sense-strand near-matches for the *EWSR1* reagent at a deeper search ceiling than the default, against eight for the *TAF15* one. Most of the 123 are predicted transcript models rather than curated records, so the count is a search result over a database that includes predictions, not a census of expressed transcripts. The *EWSR1* reagent also carries a sense-strand near-match in wild-type *TAF15* precursor RNA at two mismatches, one inside the catalytic gap, spanning an intron-exon boundary: the cost of the same ten shared donor bases that let one oligonucleotide span the *EWSR1*, *TAF15* and *FUS* breakpoints at once (Figure 1). The *TAF15* reagent carries

no sense-strand precursor site. Both loads are predictions from sequence search rather than measured activity.

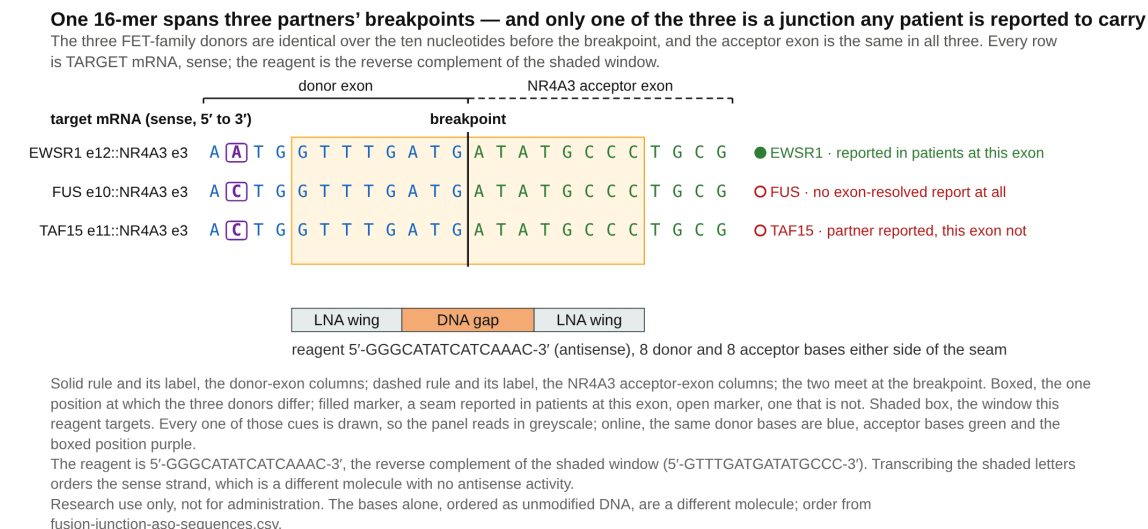


Figure 1. One 16-mer spans three partners' breakpoints, and only one of the three is a junction any patient is reported to carry. The junction windows of *EWSR1* exon 12, *TAF15* exon 11 and *FUS* exon 10 joined to *NR4A3* exon 3, aligned at the breakpoint, each row carrying its own reporting status. The *TAF15* row is exon 11 — a different junction from Table 1's *TAF15* exon 6 reagent, and one of the two further breakpoints the *EWSR1* reagent also spans. No reagent is named at it.

Both reagents are phosphorothioate throughout, with wings of five contiguous β -D-oxy-LNA residues — a high locked content against the two to four per wing taken here as usual, so these are not conventional LNA reagents and their matched-duplex melting temperatures are correspondingly high. That cuts against the screens: a high-affinity chemistry is reported to retain knockdown at more extensively mismatched sites than a conventional design does^[12], so the two-mismatch ceiling the near-match screens run at may under-call for reagents of this locked content. Both begin 5'-GGG, a contiguous locked G-tract. High affinity is taken to carry a risk of sequence-dependent hepatotoxicity; that is a premise adopted here rather than a retrieved finding, and nothing here measures it.

Discounted by the breakpoint distribution of an 18-case series^[16], the two junctions account for 68.4% of molecularly confirmed cases in a 58-case cohort^[17]. That prices which published junctions the two reagents address; it is not a coverage measurement, no patient having been screened with either

sequence. The range 39.9% to 82.8% quoted with it is not a confidence interval and carries no nominal level: two of its four inputs do not vary, and it assumes a breakpoint distribution reported in one cohort transfers to a second collected twenty-one years later. The *TAF15* arm is priced at three of three reported breakpoints, an upper bound rather than an estimate.

That figure is not a ceiling: a third design, 5'-GGGCATATCTCCACGG-3' at *EWSR1* exon 13 joined to *NR4A3* exon 3, already tiled and screened at the same top margin, would take the figure above to 79.0%. It is not named for synthesis: this junction is third by reported prevalence and the selection above takes the first two.

Selection from a panel of 190 designs

Two bounds apply to the cleanliness counts below, and to those alone. Seven of the 190 alignment screens never returned, so counts from that screen are taken over the 183 that did. That screen also censors its own hit lists, leaving 47 of those 183 assessable for cleanliness, so a count of clean designs is a floor over that subset rather than a panel total. Most designs clean at the default ceiling are not clean at a deeper one. The mature-parent screen is a sequence computation, not a database query: it ran on all 190, and the counts that follow carry neither bound.

The two reagents above survived a screen applied uniformly to the whole panel. Across the 38 in-frame junctions of five modelled partners, 190 designs were tiled and put through five specificity screens. Of those, 87 let one of six mature wild-type parent transcripts pair their entire catalytic gap over a contiguous duplex of at least ten base pairs, and 61 of the 87 do so against wild-type *NR4A3*; 85 are paired by one of the design's own two parent genes. A second class is invisible to any screen over mature transcripts: 19 designs carry a sense-strand near-match in parent precursor RNA pairing the gap in full. As a union rather than a sum the two screens condemn 93 of the 190. A design whose gap carries a mismatch is scored zero rather than short, so the 87 bound the fully-paired class, not the whole parent liability. Re-scored on duplex stability rather than on mismatch count, 8 designs carry a fully paired sixteen-base-pair off-target duplex and 45 one inside 2 kcal/mol of their own; neither named reagent is in either class, the closest to each being 3.2 and 3.0 kcal/mol weaker.

Lengthening the catalytic gap does not remove this liability, for an arithmetic reason: every base inside the gap comes from the donor or the acceptor exon, so a longer gap buys margin only by conceding parent-paired gap DNA at the design's own seam. Across three geometries the liable count does not fall; the archived deposit gives the series.

Three designs clear every screen applied here, none at a junction any patient is reported to carry, which makes them mechanism controls rather than candidates. Selecting within each junction rather than across the panel is what makes the two named reagents available: 35 of the 38 junctions have a design clearing the parent screen, and all five junctions with a published exon-resolved breakpoint have one. Both readings are properties of the cut. At nine base pairs 31 of the 38 still clear and three of the five published ones do; at eight, 23 and two; at seven, 9 and none; at six, 6 and none. These are whole-duplex run lengths rather than the enzyme's own unit, and the availability the named reagents rest on fails at nine, where the *TAF15* junction's best design is itself liable. As design counts the loose cuts condemn almost everything: 175 of 190 at seven and 181 at six.

The comparison against null models does not resolve an excess specific to this disease. Mononucleotide scrambles meet the parent screen at 6.2% against 45.8% for the panel. They are the weakest of the ten nulls screened, and not the dinucleotide-preserving control prescribed below. Chimeras built at real exon termini of the same two transcripts, at junctions almost never reported in a patient, meet it at 40.6%. The adopted cut does not escape that comparison: at ten the strongest null's 40.6% falls inside the panel's own 95% interval on 45.8%, as at every cut from seven to thirteen but eleven, and the strongest null reaches 91.4% at seven against the panel's 92.1%. The comparison is narrower than it reads, the panel arm being itself mostly unreported junctions — the property the chimeric null is discounted for. Most of the liability is therefore what joining two exon termini of these genes gives, and across cuts of six to thirteen base pairs the excess over the strongest null changes sign four times.

Test articles

Five test articles bear on the junctions this panel designs against, and they divide into two sources with opposite limits. Every design in the panel joins its donor to *NR4A3* exon 3, its first coding exon; the two cell models are reported at exon 2, and annotation does not reconcile the two. On all four annotated *NR4A3* transcripts, the three with a RefSeq accession included, exon 3 is the first coding exon and exon 2 is non-coding, so a reported exon-2 acceptor is not this panel's acceptor renumbered.

That mismatch is a property of how the panel was selected, not of the disease. Its 38 junctions were graded for a fusion protein, so an acceptor upstream of the *NR4A3* initiation codon was dropped as non-coding. That is the right filter for a degrader or a neoantigen and the wrong one for an RNase-H1 gapmer, which cleaves a transcript whether or not its reading frame survives. Exon 2 is a sequenced acceptor in this disease: *EWSR1* exon 7 joined to *NR4A3* exon 2 was resolved in one of five *EWSR1*-rearranged tumours

of a whole-transcriptome series^[18], and a *PGR::NR4A3* case joins exon 2 to the *NR4A3* 5' untranslated region^[19]. Beyond exon 3 the position is the reverse: across the exon-resolved *NR4A3* junctions retrieved here every acceptor is exon 2, exon 3, or a cryptic exon in intron 2^[20], none 3' of exon 3, so nothing is designed there because no patient is reported there.

Three are engineered constructs from a published functional study^[20], whose exon spans that paper states verbatim; two of them, E-N and T-N*, carry exactly the junctions the reagents above span, so both named reagents have a stated test article. Rebuilding them is the faster route, but a complementary DNA over-expressed in a heterologous background speaks to junction-selective knockdown of the intended transcript, not to activity at an endogenous locus.

The other two are patient-derived, identity-clean models reported with two EMC tumours^[21], USZ20-EMC1 (RRID:CVCL_C6MX) and USZ22-EMC2 (RRID:CVCL_C6MY) — the only source of a fusion-positive EMC cell identified here. They are available on request with no repository deposit, at reported doubling times of five to six days. Their fusions are reported as *EWSR1* exon 13 and *TAF15* exon 6 joined to *NR4A3* exon 2 rather than exon 3. The report carries no sequenced exon-exon boundary, no transcript accession and no junction sequence, so whether that names a non-coding acceptor or an unsupported numbering is not decidable from what is published. This work's own withdrawn version arose from an error of exactly this class.

One reading is nonetheless more parsimonious. EMC's defining lesion produces a chimeric transcription factor^{[1][20]}. A donor joined to *NR4A3*'s non-coding exon 2 would sit upstream of that gene's own initiation codon and so would not yield one — though it would leave that codon intact and place *NR4A3* under the donor's promoter, a lesion of another kind rather than none. A donor joined to the first coding exon — transcript exon 3 — does yield a chimera. On that reading USZ22-EMC2 carries the junction the *TAF15* reagent spans, and USZ20-EMC1 carries *EWSR1* exon 13 joined to exon 3 — the third design named above, not a reagent named for synthesis. This is an inference and not a determination, and the requirement below is unchanged. Reagents exist at both acceptors: 5'-AGTGGGCTCTCCACGG-3' at *EWSR1* exon 13 to exon 2 and 5'-AGTGGGCTCTTGTGTG-3' at *TAF15* exon 6 to exon 2, both at the panel's top margin. Neither reaches the ten-base-pair criterion, and their longest wild-type parent duplexes through the whole gap are eight base pairs against wild-type *EWSR1* and nine against wild-type *NR4A3* — the second against the acceptor parent on which the selectivity ratio is defined, a closer call than either exon-3 reagent presents. A reagent selected for one acceptor is not valid for the other.

One requirement is upstream of all of them: the breakpoint of the test article must be established at nucleotide resolution by RNA sequencing before any oligonucleotide is ordered, every design here being specific to the exon pair it was tiled at. Routine diagnosis does not supply the seam, since break-apart *NR4A3* fluorescence in situ hybridisation detects a rearrangement irrespective of partner^[3].

Controls for the knockdown experiment

Two controls are named as sequences (Table 2): a dinucleotide-preserving scramble of each reagent, drawn and then put through the same mature-parent screen the reagent passed. That screening is what makes a scramble a control — 10.0% of such scrambles pair a parent's whole catalytic gap at the ten-base-pair criterion and 3.9% do so against wild-type *NR4A3*, so an unscreened one carries a one-in-ten chance of being a second active molecule offered as a negative control. Clearing the screen is not a claim of inertness; it is the property a negative control has to have.

Discussion

The falsification experiment

An isogenic fusion-positive against fusion-negative comparison has been run in an analogous fusion sarcoma, against *NAB2::STAT6* in solitary fibrous tumour^[22]. It is specified here for these reagents, with three controls a knockdown assay alone cannot distinguish, two of them the screened scrambles above.

Selectivity is the wild-type *NR4A3* half-maximal knockdown concentration divided by the fusion's, from a matched dose-response in the same wells, at a cut of 5.0 adopted as a convention. Comparing the two half-maximal concentrations is the margin assessment the recommendations specify at this step; they decline to set a default value for it^[12]. At an assumed replicate standard deviation of 0.35 on the natural-log scale — a 1.42-fold replicate spread, and like the cut adopted for pre-registration rather than measured here — six independent biological replicates give about 80% power to falsify a true selectivity of 3 and three give about 30%. Above a realised standard deviation of about 0.65 at three replicates — 1.53 at six, 2.25 at ten — no observed ratio at or above one can put the upper limit of a two-sided 95% interval below 5, so the test can fail only on an anti-selective reading. Those figures are computed on that interval; a normal-approximation interval would move them. Such a test is void. Voidness is a property of the realised variance rather than of the design, so a pilot-based gate on the population variance bounds it from one side only. Where a one-sided 95% chi-square bound on the pilot's standard deviation lies at or

above the void figure for the count proposed, the decision is a larger replicate count, or no falsification test at all, and never three. The threshold is defined on the acceptor parent alone, so a reagent can clear it while pairing a donor transcript through its whole gap.

Interpretation and limits

Designability is not the constraint: a junction-spanning design exists at every junction modelled here, and 35 of the 38 have one clearing the parent screen.

The constraint is discrimination between the fusion and its parents, and it is not resolved here. A junction design's most plausible wild-type liability is its own parent, in the mature transcript or across a splice junction in precursor RNA. Both are searched before any molecule exists, but not on comparable terms: the mature-transcript screen condemns on a ten-base-pair duplex through the gap and the precursor arm on a hit at up to two mismatches with the gap fully paired, so neither restates the other. Their counts may not be added either, because a design condemned in both is one design. A third compartment is searched only in the archived deposit: the patient's own un-rearranged *NR4A3* allele, at a two-mismatch ceiling that bounds its class from below. No design this panel selects is condemned by it, but it excludes two registers of the *EWSR1* exon 13 to *NR4A3* exon-2 seam above while clearing that reagent — the register hazard noted with the reagents, arriving from a compartment the panel's selection never has to consider.

The four junction-specificity reports cited here^{[8][9][10][23]} were all made on molecules already synthesised; no survey of design pipelines was performed, so the screen-before-synthesis claim is about this literature as retrieved and not a priority claim. Whether sparing wild-type *NR4A3* is worth a specificity cost is itself unsettled, the reported paralogue redundancy and dosage effects pointing in opposite directions; the archived deposit gives that literature and does not resolve it either.

Three limits bound what any test of these reagents could show. All five screens address hybridisation rather than cleavage, and none establishes that a predicted duplex forms or is cut. The method-level novelty is nil, junction-directed oligonucleotides being long established; what is new is the indication and the screen applied before synthesis. And systemic delivery to a solid tumour remains unsolved, the gate this modality faces after any result reported here. Every source of a test article named here ends at someone culturing cells.

Tables

Every cell below is a column of fusion-junction-aso-sequences.csv, the canonical machine-readable record, except the test-article column of Table 1, which is a literature fact and carries its source in the caption. Every reagent named here is a 5-6-5 phosphorothioate gapmer. An oligonucleotide should be ordered from that file rather than transcribed from this page.

seam	reagent	WT gap duplex (bp)	test article
EWSR1 e12::NR4A3 e3	5'-GGGCATATCATCAAAC-3'	8 bp, wild-type TFG	E-N, engineered construct
TAF15 e6::NR4A3 e3	5'-GGGCATATCTTGTGTG-3'	9 bp, wild-type TFG	T-N*, engineered construct

Table 1. The two reagents named for synthesis, with their parent-duplex label and their test article. The parent-duplex column is the longest contiguous duplex a mature wild-type parent forms through the catalytic gap; neither reagent reaches the ten-base-pair criterion, so the length is printed rather than a pass mark. Test articles are the engineered constructs of Brenca et al. (PMID: 31020999); the two patient-derived models of Bangerter et al. (PMID: 36316541) are REPORTED at an NR4A3 exon-2 acceptor and match different designs, not these two. ΔT_m separates the fusion duplex from the more stable half of the design's own target window: ≥ 26.6 °C and ≥ 36.0 °C for the two rows in order, floors rather than estimates, for the reason Methods gives. Nothing here has been synthesised or tested, and no sequence may be administered to any person or animal.

control	sequence	scramble of	WT gap duplex (bp)
control-1	5'-GGGCATCAACATAATC-3'	the EWSR1 e12:: NR4A3 e3 reagent	6 bp, wild-type TAF15
control-2	5'-GTATGTCATTGGCTGG-3'	the TAF15 e6:: NR4A3 e3 reagent	7 bp, wild-type EWSR1

Table 2. The two control oligonucleotides, each screened as its reagent was. Each is a dinucleotide-preserving scramble of the reagent it controls, matching it in length, first and last base, base composition and dinucleotide counts while spanning no junction, and each cleared the same mature-parent screen the reagent did. That screening is what separates a negative control from a second active molecule; Results gives the rate at which an unscreened scramble would be one.

Notes

Running title: NR4A3 junction gapmers for EMC

Statements and Declarations

Funding

No specific funding was received for this work.

Potential Competing Interests

No potential competing interests to declare.

Ethics

Research use only, and not for administration to any person or animal. Every sequence here is a research reagent for laboratory investigation only, and none has been synthesised or tested. Order from the canonical record, fusion-junction-aso-sequences.csv, which specifies the sequence, every locked residue and the backbone, and not until the breakpoint has been established at nucleotide resolution by RNA sequencing.

Ethical considerations. Not applicable. No human subjects, human material or animals were involved, and no ethics approval was required.

Consent to participate. Not applicable. No participants were enrolled.

Consent for publication. Not applicable. The manuscript contains no data from any individual person.

Data Availability

All code, graded artefacts and per-design tables are deposited under [doi:10.5281/zenodo.22061075](https://doi.org/10.5281/zenodo.22061075). That deposit carries every screen's parameters and the complete bounds on each claim, and is the citable record for them. An earlier version of these analyses placed the acceptor junction incorrectly through a coding-versus-transcript exon indexing error and was withdrawn in full; the panels were rebuilt and verified, and the complete correction record is released with the archive.

Author Contributions

T.D.M. is the sole author, and is responsible for the conception and design of the study, the analysis code, the screens and their interpretation, and the drafting and revision of this manuscript.

Use of Generative AI

A large language model (Claude, Anthropic) was used throughout this work: to write and review the analysis code, to run the screens, to retrieve and check literature, and to draft and revise this manuscript. Every reference's bibliographic record was retrieved from PubMed rather than written from model output, and each citation was checked against the retrieved record. The author directed all work reported here and is responsible for its content.

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