



Stop Codon

Related terms:

[Exon](#), [Eicosanoid Receptor](#), [Ribosome](#), [Transfer RNA](#), [Phenotype](#), [C-Terminus](#), [Proteome](#), [DNA](#), [RNA](#), [Codon](#)

Genome Composition, Organization, and Expression

Roger Hull, in [Plant Virology \(Fifth Edition\)](#), 2014

i Stop Codon Context

Stop codons have different efficiencies of termination (UAA>UAG>UGA) and in the first, and possibly the second, nucleotide 3' of the [stop codon](#) acts as an important efficiency determinant (Stansfield et al., 1995). It can be seen from Table 6.8 that either amber (UAG) or opal (UGA) [stop codons](#) are read through; there are no examples of readthrough of the natural ochre (UAA) stop codon. However, when the suppressible UAG codon of TMV is replaced by a UAA codon, the virus can still replicate and produce mature virions (Ishikawa et al., 1986). Unlike [retroviruses](#), there appear to be no structural requirements for stop codon suppression in plant systems.

Various motifs have been recognized to stimulate readthrough (Beier and Grimm, 2001; Harrell et al., 2002). Type I (generally UAG CAA UYA) is found in tobamovirus replicase and benyvirus and [pomovirus](#) CP extension; Type II [generally UGA CGG or UGA CUA together with a 3' structure (Firth et al., 2011)] is found in [tobravirus](#), [pecluvirus](#), [furovirus](#), and [pomovirus](#) replicase and [furovirus](#) CP extension; and Type III (generally UAG G together with a compact pseudoknot) is found possibly in luteoviruses and [tombusviruses](#). Firth et al. (2011) note that there are some exceptions to these motifs (e.g., [enamovirus](#) UGA G) and that there may be modulation of readthrough by 5' sequences; this may reflect the level of readthrough required by different viruses.

The context of the TMV amber stop codon at the end of the 126-kDa ORF has been studied in detail by insertion into constructs containing the GUS or other genes which enable readthrough to be quantitated in [protoplasts](#) (Valle et al., 1992). This experimental approach has defined the sequence (C/A)(A/C)A.UAG.CAR.YYA (R=purine, Y=pyrimidine) as the optimal consensus context (Skuzeski et al., 1991; Hamamoto et al., 1993; Harrell et al., 2002). Efficiently recognized stop codons normally have a purine immediately downstream and avoid having a C residue (Fütterer and Hohn, 1996).

However, an analysis of Table 6.8 shows that the readthrough stop codons identified for plant viruses do not necessarily conform to these contexts determined from *in vitro* systems. As the sequence context differs from that described above, the readthrough of UAG.G in many of the [Tombusviridae](#) and the [Luteoviridae](#) suggest that a different mechanism might be involved. It is possible that there may be a requirement for additional *cis*-acting sequences such as a conserved CCCCA motif or repeated CCXXX motifs beginning from 12 to 21 bases downstream of many of these readthrough sites (Fütterer and Hohn, 1996; Miller et al., 1997). It may be that other long-distance interactions are involved in the deviations from the experimentally determined optimal contexts for TMV.

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Virus Interactions With the Cell

Susan Payne, in [Viruses](#), 2017

Suppression of a [stop codon](#) is a process whereby a ribosome fails to terminate [protein synthesis](#) at a [stop codon](#). Most eukaryotic genes terminate with multiple [stop codons](#), but if there is a single stop codon, an amino acid can be inserted into the growing polypeptide and translation continues. This is estimated to occur as often as 20% of the time. Thus a protein coding sequence downstream of a pseudoknot or a single stop codon will be synthesized at a lower quantity (~20%) than the protein encoded when the signal is ignored (~80% of the time).

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Mutations and Repair

David P. Clark, ... Michelle R. McGehee, in [Molecular Biology \(Third Edition\)](#), 2019

The [stop codons](#) were originally identified by mutations in [bacteriophage T4](#). The first one identified was UAG, the amber codon, which received its name in a curiously convoluted manner. The laboratory of Seymour Benzer at Caltech was looking for a mutation that would allow a certain kind of bacteriophage mutant to grow. Benzer said that whoever identified the mutation would have it named after him. The mutation was eventually isolated by a student named Harris Bernstein. Since “Bernstein” is German for “amber” UAG was named the amber codon. The second [stop codon](#) to be found (UAA) was called “ochre” to keep the color theme. The third [stop codon](#) (UGA) is less common and so the use of “opal” or less often “umber” is less frequent and not fully settled.

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Modern Molecular Therapies for Respiratory Disease

Gwyneth Davies MBChB, ... Jane C. Davies MB, ChB, MRCP, MRCPCH, MD, in [Kendig & Chernick's Disorders of the Respiratory Tract in Children \(Eighth Edition\)](#), 2012

Targeting Post-Transcriptional Regulation

[Stop codons](#) are [nucleotide](#) triplets in mRNA that serve an important role in signaling the end of protein coding sequences. Premature [stop codons](#) are those that are present in mRNA prior to their normal position in the gene. This means that the message to create the protein of interest is incomplete; thus only incomplete (commonly referred to as [truncated](#)) protein is formed. Small molecules that allow the read-through of premature stop codons are being evaluated for diseases with this genetic basis (e.g., class I mutations in [CF](#), where full-length [CFTR](#) protein is not produced).

The [aminoglycoside gentamicin](#) was initially shown to possess such capabilities, but concerns over the adverse safety profile of this group of agents (renal toxicity and sensorineural deafness) led to a search for other potential candidates. One such candidate is the oral small-molecule agent [PTC124](#) (PTC Therapeutics, South Plainfield, NJ). This was identified by a high-throughput screening process involving over 800,000 compounds. PTC124 has been evaluated in both adults and children with at least 1 [nonsense mutation](#) in CFTR in early-phase clinical trials. Changes toward normal have been seen in nasal PD measurements (a bioelectrical test of CFTR function) in the majority of adults²⁹ and in around half of children.³⁰ An increased proportion of airway epithelial cells expressing CFTR detected by

immunofluorescence was also seen.³⁰ These phase II trials involved CF patients from Israel (adults) and Europe (children). The results were in contrast to the lack of efficacy seen in a phase II trial of PTC124 in the United States.³¹ The reasons for the discrepant trial outcomes remain unknown. Multicenter phase III trials designed to assess clinical benefit are currently in progress.

Nonsense mutations leading to premature stop codons have also been found in patients with primary ciliary dyskinesia (PCD). PCD is not a single gene disorder, but mutations in the *DNAH5* gene have been found in a high number of patients, particularly those with outer dynein arm defects,^{32,33} and most are nonsense mutations. PTC124 is being investigated *in vitro* as a novel treatment for PCD. Like CF, current treatments for PCD are supportive, and therefore the theoretical advantages of this treatment approach could ultimately change management (targeting the cause rather than consequences of disease), albeit only in certain subgroups of patients.

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Molecular Therapies for Cystic Fibrosis

Gwyneth Davies MBChB, MSc, PhD, MRCPCH, ... Jane C. Davies MB ChB, FRCPCH, MD, in Kendig's Disorders of the Respiratory Tract in Children (Ninth Edition), 2019

Read-Through Agents

Stop codons are nucleotide triplets in messenger RNA (mRNA) that serve a key role in signaling the end of protein coding sequences (e.g., UAG, UAA, UGA).

Premature stop codons are those that occur within the normal coding sequence due to a mutation. This means that the message to create the protein of interest is incomplete; thus only truncated protein is formed. Molecules that allow the read-through of premature stop codons, thus enabling the production of full-length protein, are being evaluated for several diseases including class I mutation CF.

The aminoglycoside gentamicin was initially shown to possess such capabilities,⁷ but concerns over the adverse safety profile of this group of agents (renal toxicity and sensorineural deafness) led to a search for other potential candidates. The one that has been most extensively investigated is the oral small molecule drug ataluren (Translarna, formerly PTC124. PTC Therapeutics; <http://www.ptcbio.com/en/pipeline/ataluren-translarna/>). This was identified by a high-throughput screening process involving more than 800,000 compounds. In CFTR knockout mice expressing human G542X mutant CFTR, ataluren increased CFTR expression at the apical surface of epithelial cells and restored cyclic adenosine monophosphate (cAMP)-stimulated chloride currents to approximately 25% of wild type.⁸ Ataluren has been evaluated in both adults and children older than 6 years with at least one CFTR nonsense mutation. Changes toward normal in nasal potential difference (nPD) measurements (a bioelectrical test of CFTR function) were observed in most adults⁹ and in approximately half of children in early phase trials.¹⁰ An increased proportion of airway epithelial cells expressing CFTR detected by immunofluorescence was also seen.¹⁰ These phase II trials involved CF patients from Israel (adults) and Europe (children). The results were in contrast to the lack of efficacy seen in a phase II trial of PTC124 in the United States.¹¹ The phase III randomized controlled trial (RCT) that followed involved 238 patients with a nonsense CFTR mutation. Patients were randomized to receive ataluren in a 3 times daily dosing regimen (10 mg/kg morning and midday; 20 mg/kg evening) or placebo for 48 weeks.¹² Although neither the primary outcome of forced expiratory volume in one second (FEV₁) nor the secondary outcome of a reduction in pulmonary exacerbations were met, on *post hoc* analysis these outcomes were statistically significant for patients who were not receiving concurrent inhaled tobramycin as part of their routine CF management.¹² This has led to a further phase III trial (NCT02139306) specifically for patients not on inhaled aminoglycosides, as it has been suggested that the lack of response in

patients receiving aminoglycosides may be due to competition with ataluren at the ribosomal binding site; at the time of writing, the results of this second trial have not been published, but a sponsor's press release describes it as having failed to achieve its outcomes (<http://ir.ptcbio.com/releasedetail.cfm?releaseid=1015471>). Drugs such as ataluren targeting premature stop codons have the potential for broader applicability than being limited to a single disease. For example, ataluren has been granted a conditional marketing authorization by the European Medicines Agency, based on the results of a phase IIb study in boys with Duchenne muscular dystrophy in conjunction with an unmet need for disease-modifying therapies in this condition.^{13,14}

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Principles and Practice of Molecular Therapies

Louise R. Rodino-Klapac, Jerry R. Mendell, in Neuromuscular Disorders of Infancy, Childhood, and Adolescence (Second Edition), 2015

Aminoglycoside Therapy

Stop codons account for approximately 13% to 15% of DMD mutations.^{28,29} Effective treatment of this group has potential impact equivalent to exon skipping. Encouraging results were originally obtained in *mdx* mice where the aminoglycoside, gentamicin, successfully increased dystrophin expression to about 20%.³⁰ Gentamicin-treated mice showed improved histology and protection against contraction-induced injury. Plasma CK levels were also reduced by 70%. Molecular studies of mutation suppression in the *mdx* mouse served as a stimulus to attempt a similar approach using gentamicin in DMD patients. The initial clinical trial reported in four DMD patients carrying premature termination codons in the *DMD* gene reported no improvement in clinical measures or dystrophin expression. Of interest, serum CK dropped significantly.³¹ A subsequent gentamicin trial reported more favorable results in a small cohort of four subjects.³² When gentamicin was given over two cycles, each for 6 days with a 7-week hiatus between dosing, muscle biopsy revealed increased dystrophin expression in 3 out of 4 patients. Serum CK decreased from day 2 to day 6 of the treatment but subsequently came back to the initial levels. No clinically meaningful outcomes were obtained in any of these patients.

A third clinical trial conducted by our group at the Nationwide Children's Hospital consisted of a two-phase protocol.³³ An initial short-term gentamicin, 14-day dosing study was carried out in 10 DMD boys with proven stop codon mutations. A biological effect was established with a 50% reduction of CK by day 14. The results were stop codon-dependent since serum CK did not change in a control group with frameshift mutations. Having demonstrated a biological effect in the short-term trial, a 6-month study was designed with weekly or twice-weekly gentamicin administration. Enrollment was dependent on normal hearing and kidney function, and negative testing for the known A1555G mitochondrial DNA mutation in the 12S rRNA gene predisposing to aminoglycoside-induced hearing loss.³⁴ Renal function was monitored using cystatin C to avoid false negative findings related to decreased serum creatinine and creatinine clearance levels in the DMD population.³⁵ Sixteen subjects with documented stop codon mutations received weekly (N=12) or twice weekly (N=4) gentamicin. No patient demonstrated a decline in renal or hearing function except one patient given a miscalculated dose (125% of recommended) for the first 4 administrations, resulting in a transient high-frequency hearing loss that returned to normal within 3 months. Owing to the small sample size, weekly and biweekly treated patients were analyzed as one group. Twelve subjects agreed to pretreatment and posttreatment muscle biopsies. In 3 of 9 subjects, dystrophin protein increased to 13.0–15% of wild-type levels (Figure 51.5). In addition to dystrophin expression in muscle tissue, serum CK was mildly reduced after 6 months of gentamicin treatment (9851±2109 U/L to 5316±850 U/L, p=0.04). Additional clinical outcome measures were variable. The

average muscle score (AMS), which was expected to decline by 0.2 units over 6 months¹³ showed little or no change (pretreatment AMS 5.37±0.39 compared with posttreatment AMS 5.35±0.38). However, no functional outcomes were improved, such as the time to walk 30 feet, climb four standard steps, or stand from a supine position on the floor.

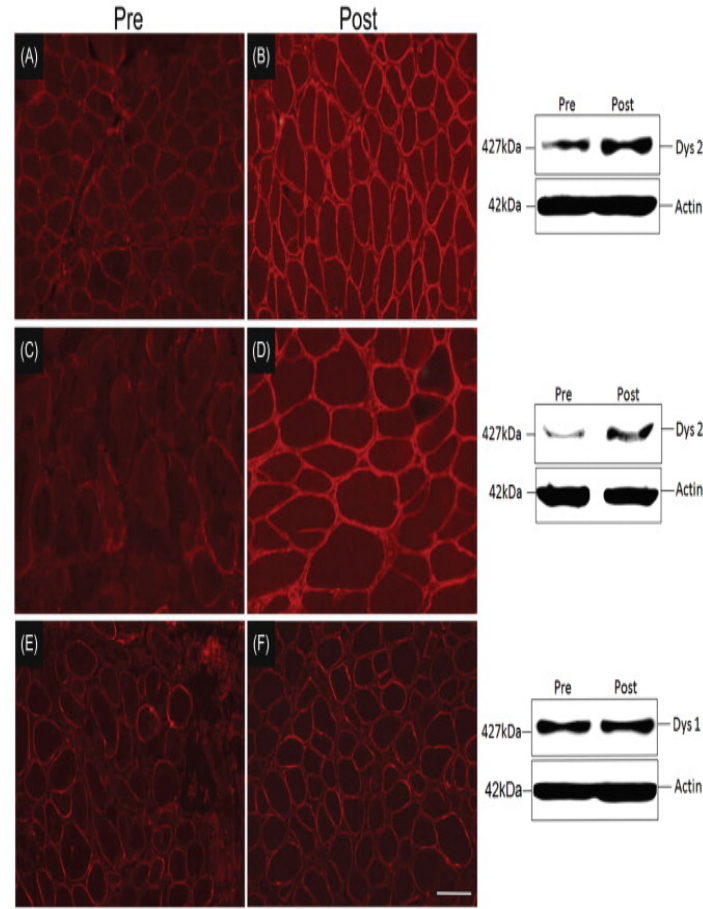


Figure 51.5. Dystrophin expression following gentamicin treatment. Pre- and post-gentamicin treatment muscle biopsies demonstrating dystrophin expression by immunofluorescence (IF) using DYS 2 Novacastra and Western blot (WB). (A, B) Pre- and post-treatment IF muscle biopsy sections (patient 6) stained with DYS2 antibody; adjacent WB shows full-length dystrophin at 427 kDa. Gentamicin–induced dystrophin expression to 15.44%. (C, D) Pre- and post-treatment muscle biopsy (patient 10) IF sections stained with DYS2 antibody; adjacent WB shows full-length dystrophin at 427 kDa. Gentamicin-induced dystrophin increased to 13.0%. (E, F) Pre- and post-treatment muscle biopsy sections from patient 5 without response to gentamicin showing negligible increase after treatment by IF and WB. Scale bar=100 μ m.

Reprinted from Malik et al., 2010.³³

Overall, the clinical trial validates that mutation suppression or readthrough can potentially be translated to patients but would require more frequent or higher dosing to produce clinically meaningful results.

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Laboratory Methods in Cell Biology

Swati Tyagi, Edward A. Lemke, in *Methods in Cell Biology*, 2013

5.1.2 Step 2—Incorporation of PrK in T4Lysozyme at Specific Position Using In Vivo Amber Suppression

The stop codon TAG is introduced at a specific residue position into the plasmid DNA sequence through site-directed mutagenesis. Cotransforming this vector with pEvol PylRS, a plasmid harboring PylRS under a strong arabinose inducible promoter, prepares the host to incorporate PrK, which is supplied to the growth media 30 min before induction of expression with arabinose. Refer to Fig. 4 for the flowchart of step 2.

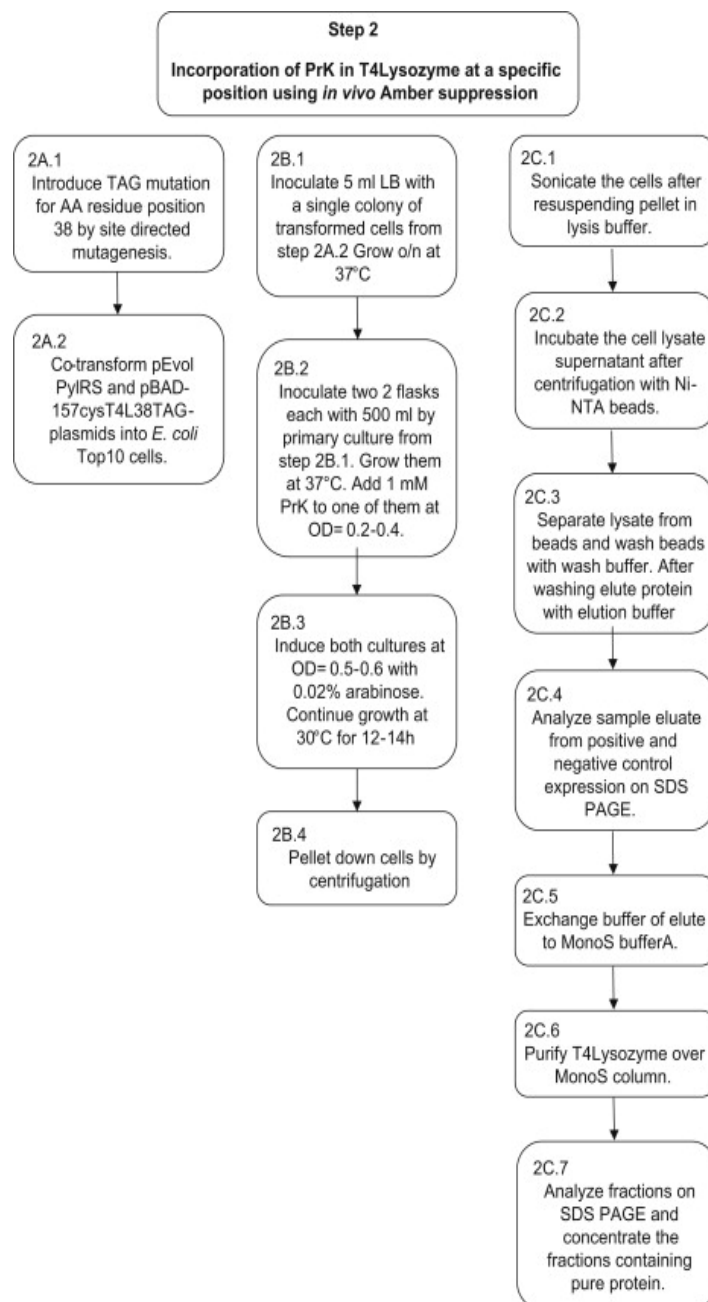


FIGURE 4. Flowchart for Step 2.

<i>Duration</i>	4 days (including cloning,)
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5.1.2.1 Step 2A—Generating Amber Mutant

- 2A.1 Perform site-directed mutagenesis to introduce the **stop codon**, TAG, for labeling by mutating the desired residue. We like to follow the mutagenesis protocol described in Zheng et al. (2004), but kits are available from various companies. In this protocol, we mutated residue 38 of T4L Lysozyme157Cys to create the plasmid pBAD-T4Lysozyme157Cys38TAG.
- 2A.2 Transform *E. coli* Top10 cells with pEvol PylRS and pBAD-T4Lysozyme157Cys38TAG and plate cells on LB agar plate with ampicillin (antibiotic resistance marker on expression plasmid for protein) and chloramphenicol (antibiotic resistance marker on pEvol plasmid). Refer to Fig. 5. Incubate plate at 37 °C for overnight.
-

5.1.2.2 Step 2B—Expression of T4Lysozyme157Cys38TAG

- 2B.1 Inoculate 5 mL of LB medium containing 50 µg/mL ampicillin and 33 µg/mL chloramphenicol with a single colony from the plate. Let it grow at 37 °C for overnight.
- Tip* To backup the clone for future expressions prepare a glycerol stock (33% glycerol with 66% of overnight culture) and store at –80 °C.
- 2B.2 Inoculate two 2 L culture flasks, each with 500 mL TB media containing 50 µg/mL ampicillin and 33 µg/mL chloramphenicol, with 500 µL of overnight culture. Grow them at 37 °C until OD₆₀₀ value reaches 0.2–0.4. Add sterile PrK solution to the growing cultures to a final concentration of 1 mM in one of the two flasks. The culture without PrK will serve as a negative control for Amber suppression.
- Tip* PrK is a stable compound and can be added right from beginning into the culture. However, addition of UAA at least 30 min before induction is recommended, which is sufficient time to prime the synthetase to charge tRNA^{Pyl} with PrK.
- 2B.3 Wait until OD₆₀₀ reaches 0.5–0.6 and then add arabinose to a final concentration of 0.02% in both flasks and let them grow for 12–14 h at 30 °C.
- 2B.4 Harvest the cells by centrifugation at 5000 rpm for 20 min. Discard the supernatant. The pellet can be stored at –80 °C for later processing.
-

5.1.2.3 Step 2C—Purification of T4Lysozyme157cys38TAG

- 2C.1 Suspend the pellet in three volumes of lysis buffer and sonicate to lyse cells.
- 2C.2 Centrifuge the lysate at 18,000 rpm, 4 °C for 1 h. Wash 1 mL of Ni-NTA bead volume with lysis buffer and incubate the supernatant for 2 h at 4 °C on the beads.
- 2C.3 Allow the lysate to pass through and collect Ni-NTA beads. Wash beads with 20 bed volumes of lysis buffer followed by 10 bed volumes of wash buffer. Elute the protein with 3 bed volumes of elution buffer.
- 2C.4 Analyze the eluate samples of the positive and negative control on SDS PAGE. After Coomassie staining, the negative sample will show no band at
-

the corresponding height for the protein as compared to the positive sample. This will confirm the successful and selective incorporation of PrK in T4Lysozyme. Refer to Fig. 5.

- Tip** In the absence of UAA, loose binding of natural amino acids in the AA-binding pocket of PylRS can cause Amber suppression, which can account for observation of a less-intense band also at the expected size for the negative control, which is frequently not a concern. If there is an equally strong band for the negative control, this might indicate that either site-directed mutagenesis to TAG codon or that Amber suppression was not successful. If protein expression for the positive sample is not satisfactory, expression can be tried at different conditions including host strain, temperature, and expression time, as well as increasing concentrations of PrK. Also, testing alternative mutagenesis sites can alleviate the problem.
- 2C.5 Concentrate the eluate for the positive sample in a centrifugal filter and exchange the buffer to MonoS buffer A. Precipitate will appear; discard it as it contains impurities that are insoluble at pH 6.3 (Steps 2C.5–2C.7 are specific for T4Lysozyme and other proteins might require other purification conditions).
- 2C.6 Load 1 mL of the sample onto a MonoS column using FPLC purification system. Apply the gradient of 100% MonoS buffer A to 100% MonoS buffer B over 30 min. This purification is based on cation exchange purification. T4Lysozyme elutes at approximately 60% salt gradient.
- 2C.7 Analyze eluate fractions on SDS PAGE and pool the fractions containing pure protein. Concentrate the fractions and determine the protein concentration on a UV/VIS spectrophotometer.

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URL: <https://www.sciencedirect.com/science/article/pii/B9780124072398000094>

Dystrophinopathies

John F. Brandsema, Basil T. Darras, in Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease (Sixth Edition), 2020

Stop codon read-through

Suppression of **stop codons** (applicable to mutations leading to premature stop in about 10%–15% of **DMD** patients) has been demonstrated with **aminoglycoside** treatment of cultured cells; the treatment creates misreading of RNA and thereby allows alternative amino acids to be inserted at the site of the mutated stop codon.⁶ Results in preclinical and clinical studies were largely negative.^{202–204}

Ataluren (**PTC124**) is an orally administered nonantibiotic drug that appears to promote ribosomal read-through of nonsense (stop) mutations to allow bypass of the pathogenic variant and continuation of the translation process to production of a functioning **dystrophin protein**. Preclinical studies through phase II studies were promising; a multicenter 48-week double-blind placebo-controlled trial (ACT DMD) showed no significant benefit of ataluren for the primary endpoint (i.e., change from baseline in the 6-minute walk test), though there was benefit for some secondary endpoints and the lower dose was favored as affected individuals on low doses of ataluren had a 30-m lower decline in the 6-minute walk distance than those on high doses or placebo.^{48,205}

Based on these results, the drug was granted conditional approval as Translarna by the European Medicines Agency in August 2014 to treat DMD caused by a nonsense variant; ataluren has not been approved for treating DMD in the United States through 2018.⁴⁸

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RNA and the Cellular Biochemistry Revisited

Robert E. Farrell Jr. Ph.D, in [RNA Methodologies \(Fourth Edition\)](#), 2010

Trailer sequence

Beyond the [stop codon](#) lies another non-translated area known as the trailer sequence or simply the 3' UTR. This sequence usually ranges from 50–150 [nucleotides](#) long, although trailer sequences as long as 1000 bases have been reported. Further, different mRNA molecules encoding the same polypeptide may differ only with respect to the length of their 3' trailer region, of which [dihydrofolate reductase](#) mRNA is one example (Will and Dolnick, 1989; Kubo *et al.*, 2006). Although no function has yet been ascribed to the trailer region, it is believed to influence the stability of the molecule in the cytoplasm due to *cis*-acting elements which bind various proteins and that may also influence mRNA localization. It is worth noting that most trailer regions manifest a highly conserved AAUAAA sequence within 30 nucleotides of the location where the synthesis of the poly(A) tail will begin (Proudfoot and Brownlee, 1976). Newer evidence suggests that [microRNA](#) (miRNA) molecules may target the trailer sequence and, in so doing, influence gene expression (Lai, 2002).

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Fidelity and Quality Control in Gene Expression

Marina V. Rodnina, in [Advances in Protein Chemistry and Structural Biology](#), 2012

C Fidelity of Peptide Release

The intrinsic fidelity of [stop-codon](#) recognition by RF1 and RF2 is quite high: the catalytic proficiency of the factors (expressed in terms of k_{cat}/K_M) is decreased by three to six orders of magnitude by single base exchanges (Freistroffer *et al.*, 2000). Assuming similar concentrations of RFs and individual aa-tRNAs (Bremer and Dennis, 1987), this predicts a frequency of sense-codon misreading of $< 10^{-3}$ and in most cases close to 10^{-5} . This high fidelity of stop-codon recognition is achieved without proofreading, presumably in a single selection step, and is due to the specific structural match between the recognition motifs of RF1/2 and their cognate [stop codons](#) (Weixlbaumer *et al.*, 2008; Korostelev *et al.*, 2010). For both RFs, the K_M values contribute close to three orders of magnitude to the accuracy with relatively small variations between different codons, providing a dominant contribution to the discrimination against near-cognate codons (Freistroffer *et al.*, 2000); in other words, RFs simply do not bind to the sense codons. This is possible because the [hydrolysis](#) reaction that leads to peptide release is much slower than the preceding recognition reactions (Freistroffer *et al.*, 2000; Youngman *et al.*, 2007; Kuhlencoetter *et al.*, 2011), and hence the intrinsic thermodynamic differences between cognate and near-cognate complexes can be used in full. However, the k_{cat} values on near-cognate codons vary significantly as well, accounting for a twofold to more than 1000-fold reduction in the rate of hydrolysis (Freistroffer *et al.*, 2000), suggesting that the structure of the RF1/RF2 complexes on stop codons and sense codons are different. In fact, biochemical studies indicated that stop-codon recognition by RFs induces a structural rearrangement of the decoding center that is productive for peptide release (Youngman *et al.*, 2007). RF3 decreases the fidelity of near-cognate codon recognition by RF1 and RF2 (Freistroffer *et al.*, 2000); however, the effect is much larger when a mismatched peptidyl-tRNA is present in the [P site](#) (Zaher and Green, 2009a,b).

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