Background

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What is Protein Synthesis?

Protein synthesis is the process whereby amino acids are linked together to form proteins using mRNA as a template.

Overview

The production of proteins from an mRNA template is a multistep process that includes:

- Activation of amino acids to allow them to be joined together
- Initiation of translation by binding of translation machinery to the mRNA template
- Elongation of the protein by successive addition of amino acids
- Termination and release of the mRNA template
- Folding and posttranslational processing of the final protein

As each step in the process relies on numerous essential components, protein synthesis is susceptible to inhibition at multiple stages. Because the translation machinery differs slightly between prokaryotic and eukaryotic organisms, bacterial translation machinery can be selectively targeted for inhibition. As a result, protein synthesis is the most common mechanism of action for naturally occurring antibiotics. Interestingly, because the mitochondria of eukaryotic cells often have bacteria-like translation machinery, off target effects in human cells can occur.

Existing Products

Existing protein synthesis inhibitors are primarily used as antibiotics, although some of these antibiotics also have anti-parasitic effects.

Product	Indication	Notes
Tetracycline (natural product)	Broad spectrum antibiotic	Prevents addition of new amino acids to a protein by occupying an important transfer RNA binding site on the 30S bacterial ribosome.
Chloramphenicol	Broad spectrum antibiotic	Prevents formation of bonds between amino acids through interactions with the 50S bacterial ribosome. Also inhibits protein synthesis in mitochondria of mammalian cells.
Streptomycin	Tuberculosis	First antibiotic ever used to successfully treat tuberculosis. Binds the 30S component of the bacterial ribosome.

Doxycycline (synthetic derivative of tetracycline)	Broad spectrum antibiotic; used for malaria prophylaxis in travelers; used off label for the treatment of filarial worms (lymphatic filariasis and onchocerciasis)	Doxycycline has the same mechanism of action as tetracycline in bacteria.
Paromomycin	Amoebiasis and leishmaniasis	Paromomycin inhibits protein synthesis by binding to 16S rRNA, part of the 30S bacterial ribosome. In eukaryotic pathogens such as amoeba and leishmania, the drug appears to bind to the equivalent site on the eukaryotic ribosome, although the mechanism of action has not been fully elucidated.

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Protein Synthesis Inhibitors as Broad Spectrum Antibiotics

Differences between eukaryotic (i.e., human, animal, protozoan parasite, helminth) and prokaryotic (i.e., bacterial) translation machinery facilitate selective or semi-selective inhibition of the prokaryotic machinery with antibiotics. The bacterial 70S ribosome consists of two subunits, the larger 50S subunit and the smaller 30S subunit. Eukaryotes, on the other hand, have an orthologous, although more complex, 80S ribosome consisting of the larger 60S subunit and the smaller 40S subunit. The majority of inhibitors of protein synthesis in bacteria target the 30S or 50S subunits of the bacterial 70S ribosome with minimal cross reactivity with the eukaryotic ribosome. However, as eukaryotic mitochondria have bacteria-like ribosomes some cross reactivity can occur.

Protein Synthesis Inhibitors as Neglected Tropical Disease Therapeutics

Streptomycin, an antibiotic derived from the actinomycete *Streptomyces griseus*, was the first antibiotic successfully used to treat tuberculosis. The compound, like many antibiotic protein synthesis inhibitors, binds to the 30S subunit of the bacterial ribosome. Although drug resistance has ultimately limited the usefulness of streptomycin for the treatment of tuberculosis, streptomycin provides proof of concept that protein synthesis is a viable therapeutic target for the treatment of tuberculosis.

The mechanism of action of protein synthesis inhibitors in protozoan parasites, such as the parasites that cause malaria and leishmaniasis, is not as well understood. The parasites that cause malaria and leishmaniasis have eukaryotic 80S ribosomes in their cytosol. Additionally, the malaria parasite has a unique organelle called an apicomplast that shares many properties with both bacteria and the plant organelle known as a chloroplast. The apicomplast has its own translation machinery including a 70S-like ribosome. The efficacy of doxycycline for the prophylactic treatment of malaria is thought to involve inhibition of this 70S-like apicomplast ribosome thus blocking synthesis of important apicomplast proteins.[1]

The efficacy of paromomycin for the treatment of leishmaniasis appears to be less straight forward. Although paromomycin is known to inhibit a subcomponent of the 30S ribosome of bacteria, biochemical studies in leishmania parasites suggest that paromomycin inhibits both cytosolic (eukaryotic) and mitochondrial (prokaryotic-like) ribosomes.[2] Biochemical studies of paromomycin on leishmania parasite ribosomes suggest that the drug preferentially binds the leishmania ribosome over the human ribosome.[3] However, paromomycin may have additional effects on membrane permeability that also contribute to its efficacy.[2]

The final group of neglected tropical diseases for which protein synthesis inhibitors have been used is in the treatment of filarial worms, a subset of parasitic worms or helminths that includes the parasites that cause lymphatic filariasis and onchocerciasis. Filarial worms are colonized by commensal bacteria of the genus *Wolbachia*. These commensal bacteria are essential for the production of microfilaria, the circulating form of the parasite that is transmitted by mosquitoes, and for the survival of the adult worms (macrofilaria) that produce the microfilaria. Clinical trials have demonstrated the efficacy of doxycycline against both the microfilaria and macrofilaria worms.[4,5] Doxycycline is not in widespread use for lymphatic filariasis or other filarial worm infections, but these studies served as an important proof of concept that the commensal *Wolbachia* bacteria are a good target for future therapeutic development.

References

1. Dahl EL and Rosenthal PJ (2008) “Apicomplast translation, transcription and genome replication: targets for antimalarial antibiotics.” *TRENDS in Parasitology* **24**: 279-284.
2. Jhingran A et al. (2009) “Paromomycin: Uptake and resistance in Leishmania donovani.” *Molecular and Biochemical Parasitology* **164**: 111-117.
3. Fernandez MM et al. (2011) “Differential effects of paromomycin on ribosomes of *Leishmania mexicana* and mammalian cells.” A*ntimicrobial Agents and Chemotherapies* **55**: 86-92.
4. Hoerauf A et al. (2003) “Doxycycline as a novel strategy against bancroftian filariasis-depletion of Wolbachia endosymbionts from *Wuchereria bancrofti* and stop of microfilaria production.” *Med Microbiol Immunol (Berl)* **192**: 211–216.
5. Taylor MJ (2005) “Macrofilaricidal activity after doxycycline treatment of *Wuchereria bancrofti*: a double-blind, randomised placebo-controlled trial." *The Lancet* **365**: 2116–2121.

Get Involved

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Pipeline & Analysis

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PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Paromomycin - Africa	Drugs for Neglected Diseases Initiative Leishmaniasis East Africa Platform					
PNU-100480	Pfizer Inc. Special Programme for Research and Training in Tropical Diseases					
AZD5847	AstraZeneca					
LeuRS inhibitor	Anacor Pharmaceuticals, Inc.					

ANALYSIS

Protein synthesis inhibitors are in development for tuberculosis and leishmaniasis. As protein synthesis is a biological process that occurs in all organisms, further exploration of protein biosynthesis machinery as therapeutic targets for neglected tropical diseases is warranted. However, inhibitor selectivity for the machinery of the neglected tropical disease over the machinery of the human host will be essential.

The relative strengths, weaknesses, opportunities, and risks for natural products that are currently in use or in development for neglected tropical diseases are summarized here.

	Strengths	Weaknesses	Opportunities	Risks
Nitroimidazoles				
Relevant neglected tropical diseases: Tuberculosis (multiple on market products; PNU-100480, phase II; AZD5847, phase I) Leishmaniasis (paromomycin, on market but currently in clinical trials as part of combination therapies)	Well proven drug target across multiple diseases Multiple on market products already in use, especially for bacterial infections	Potential off target effects in human cells	Identification of selective inhibitors of protein synthesis machinery for additional neglected tropical diseases New combination therapies	Products with the same mechanism of action are already on market Drug resistance is common for on market antibiotics using this mechanism of action

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Tools

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Databases/Resources

There are several online resources providing information on protein synthesis inhibitors including:

- Microbiologyprocedure.com - Section on inhibition of protein synthesis
- University of South Carolina Microbiology and Immunology On-line - Bacteriology Chapter 6

Assays

Monitoring protein synthesis activity generally involves monitoring incorporation of C14-labeled radioactive amino acids.[1] There are numerous cell-free systems that can be used to monitor protein synthesis, some of which have been adapted for high throughput screening.[2-4]

References

1. Martin R (ed.) Protein Synthesis: Methods and Protocols, 1998. Book information is available here.
2. Boddeker N et al. (2002) “Characterization of a novel antibacterial agent that inhibits bacterial translation.” *RNA* **8**: 1120–1128.
3. Novac O et al. (2004) “Inhibitors of protein synthesis identified by a high throughput multiplexed translation screen.” *Nucleic Acids Research* **32**: 902-915.
4. Promega Protocol and Applications: Protein expression, available here.

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Product Details

AZD5847

Synonyms:
AZD5847

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Protein synthesis

Mechanism of Action:

Molecule Class:
Oxazolidinone

Administration Route:
Oral

Notes:

More information on this product is available from the Working Group on New TB Drugs.

Clinical Trials:

NCT01037725
NCT01116258

Publications:

LeuRS inhibitor

Synonyms:
LeuRS inhibitor

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Protein synthesis

Mechanism of Action:
LeuRS inhibitor

Molecule Class:

Administration Route:

Notes:

More information on this product is available from the Working Group on New TB Drugs.

Clinical Trials:

Publications:

Paromomycin - Africa

Synonyms:
Paromomycin
Paromomycin - Africa

Disease:
Leishmaniasis

Specific Indication:
Visceral (VL)

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Protein synthesis

Mechanism of Action:

Molecule Class:
Aminoglycoside

Administration Route:
IM

Notes:	Clinical Trials:	Publications:
	NCT00255567	

PNU-100480

Synonyms:
PNU-100480
Oxazolidinones

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Protein synthesis

Mechanism of Action:
70S Ribosome

Molecule Class:
Oxazolidinone

Administration Route:

Notes:	Clinical Trials:	Publications:
More information on this product is available from the Working Group on New TB Drugs.	NCT00990990 NCT00871949	20629533 21078950