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What is Lipid Biosynthesis?

Lipids are important for energy storage, membrane integrity, hormones, signaling, and numerous other biological functions. Lipids come in several forms including fatty acids, triglycerides, phospholipids, and cholesterol.

Overview

Lipids come in several forms including those that are generated by distinct biosynthetic pathways:

- Fatty acids
- Triglycerides
- Phospholipids
- Sterols

Fatty acids are long chain hydrocarbons synthesized by the iterative addition of malonyl-CoA to an acyl chain on an acyl carrier protein. This process is carried out by the enzymes acetyl-CoA carboxylase (ACCase) and fatty acid synthase (FAS). FAS enzymes come in two forms: (1) FAS I is a multi-enzyme complex primarily found in mammals, fungi, and plants, and (2) FAS II is a series of separate enzymes that recapitulate the enzymatic activities of the FAS I complex and are primarily found in bacteria and several parasitic protozoa. Fatty acids are important building blocks for more complex lipids.

Triglycerides (or triacylglycerols) and phospholipids are the primary fate of fatty acids. Triglycerides are a major form of energy storage while phospholipids are a major component of lipid membranes. A variety of triglycerides and phospholipids with different functions and fates can be produced depending on the fatty acids that are incorporated and the enzymatic pathways utilized.

Cholesterol is a lipid that is synthesized in the liver, transported in the bloodstream, and used in the construction of cell membranes in animals. Ergosterol is the fungal equivalent to cholesterol. These and other sterols use acetyl-CoA as a primary building block. Synthesis of cholesterol and ergesterol involves more than 20 steps and a variety of enzymes including: mevalonate pathway, isoprenoid pathway, condensation of isoprene to squalene, and cyclization of squalene to lanosterol. Lanosterol can then be converted to cholesterol (animals), stigmasterol (plants) or ergosterol (fungi and several parasitic protozoa).

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Existing Products

There are numerous lipid biosynthesis inhibitors that are approved or in late stage clinical development for a variety of diseases.

Lipid Biosynthetic Pathway	Target Name	Development Status
Melvonate pathway	HMGCoA reductase	Multiple Statins, FDA approved for lowering LDL-cholesterol

Lanosterol conversion to ergosterol	CYP51	Posoconazole (Merck), FDA approved for invasive fungal disease
Fatty acid synthesis	FAS II	Isoniazid and ethionamide, FDA approved for tuberculosis
	FAS I	Pyrazinamide, FDA approved for tuberculosis

Lipid Biosynthesis Inhibitors as Non-Neglected Tropical Disease Therapeutics

There are several diseases that are not related to neglected tropical diseases for which lipid biosynthesis has been targeted, including atherosclerosis/heart disease and fungal infections.

Statins are inhibitors of the enzyme HMGCoA reductase, a key biosynthetic enzyme in the melvonate pathway that is utilized for the production of cholesterol in humans. High levels of low density lipoprotein (LDL)-cholesterol can lead to the formation of fatty plaques in the arteries, also known as atherosclerosis, and eventually heart disease. HMGCoA reductase inhibitors are the cornerstone for the treatment of high LDL -cholesterol and several products have demonstrated the ability to prevent heart attack and stroke as a result of their effects on LDL-cholesterol.

Fungi produce ergesterol as a primary sterol. This is in contrast to humans and other mammals that produce primarily cholesterol. Although fungi that infect humans may salvage some cholesterol from the host, this is not sufficient to replace de novo ergesterol biosynthesis. The enzyme C14alpha-demethylase (CYP51) is involved in both ergesterol and cholesterol biosynthesis. Inhibitors of CYP51 have been used successfully to treat invasive fungal infections in humans.[1] Although CYP51 inhibitors may also inhibit some cholesterol biosynthesis in humans, they do not significantly decrease cholesterol levels since the majority of human cholesterol comes from diet rather than de novo synthesis.

Lipid Biosynthesis Inhibitors as Neglected Tropical Disease Therapeutics

Lipid biosynthesis has been targeted for antibacterial development due to differences between bacterial and mammalian fatty acid biosynthesis. Mycolic acids are long chain fatty acids that are unique to the cell wall of a group of bacteria that includes Mycobacterium tuberculosis, the bacterium that causes human tuberculosis. *M. tuberculosis* is particularly interesting because it uses both FAS I and FAS II pathways to produce mycolic acids.[2] Isoniazid (INH) is the cornerstone of first line tuberculosis treatment. INH inhibits an enzyme in the *M. tuberculosis* FAS II pathway InhA, an enoyl acyl carrier protein reductase. Inhibition of InhA interferes with the synthesis of the mycobacterial cell wall. Pyrazinamide (PZA) inhibits the *M. tuberculosis* FAS I pathway and is used as part of combination therapies with INH and rifampicin for the treatment of tuberculosis.

The success of FAS I and II inhibitors for the treatment of tuberculosis suggests exploitation of differences in fatty acid and other lipid biosynthetic pathways between mammalian, bacterial, and parasitic organisms is a viable strategy for future neglected tropical disease drug development.

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References

1. de Souza W and Rodrigues JC (2009) “Sterol biosynthesis pathways as target for anti-trypanosomatid drugs.” *Interdisciplinary Perspectives on Infectious Diseases* **2009**: 642502.
2. Schroeder EK et al. (2002) “Drugs that inhibit mycolic acid biosynthesis in Mycobacterium tuberculosis.” *Current Pharmaceutical Biotechnology* **3**: 197-225.

Get Involved

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Pipeline & Analysis

Get Involved

PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
Posaconazole	Hospital Vall d'Hebron Merck & Co., Inc.					
Sudoterb	Lupin Pharmaceuticals, Inc.					
E1224	Drugs for Neglected Diseases Initiative Eisai Inc.					
TAK-187	Takeda Pharmaceutical Company LTD					
InhA inhibitors	GlaxoSmithKline Global Alliance for TB Drug Development					
ND701	NeED Pharma					
Lanosterol demethylase inhibitors	Consortium for Parasitic Drug Development Georgia State University The University of North Carolina at Chapel Hill					
FAS 20013	FASgen		On Hold			
Pyrazinamide analogs	Global Alliance for TB Drug Development Yonsei University	On Hold				

ANALYSIS

Inhibitors of biosynthetic pathways have been validated as therapeutic targets for a variety of diseases. As a target class, lipid biosynthetic pathways benefit from an extensive body of existing research into the understanding of their catalytic mechanisms, reaction mechanism, and structures. Additionally, inhibitors of lipid biosynthetic pathways have the potential to benefit from the recycling of chemical compound libraries developed through previous drug development programs.

The relative strengths, weaknesses, opportunities, and risk for lipid biosynthesis inhibitors that are currently in development for neglected tropical diseases are summarized here.

	Strengths	Weaknesses	Opportunities	Risks
Sterol biosynthesis: Downstream of isoprenoid pathway				
Relevant neglected tropical diseases: Chagas (posaconazole, phase II; E1224 and TAK187, phase I) Leishmaniasis	Posaconazole is already on market as an antifungal All of the clinical stage products in this category have unique mechanisms of action	No clinical trial data for efficacy in parasitic diseases are available yet One of the targets of ND701 for tuberculosis, CYP51, is non-essential	Potential for application of products discovered through these programs across multiple neglected tropical diseases Addition of new products to drug combinations	Host toxicity may be an issue

(lanosterol demethylase inhibitors, discovery Tuberculosis (ND701, discovery)	relative to on market products for the neglected tropical diseases listed here	in that As many of the targets in this pathway have mammalian homologs host toxicity must be carefully evaluated	Exploration of new targets from this pathway	
Fatty acid biosynthesis: FAS II				
Relevant neglected tropical diseases: Tuberculosis (INH and ETH on market; multiple programs, discovery through phase II)	Based on well-established existing drugs for tuberculosis treatment	Drug resistance and liver toxicity are common with INH, so related compounds may not overcome these weaknesses	Application of compounds from tuberculosis programs to protozoan neglected tropical diseases that also have FAS II pathways Addition of new products to drug combinations	High risk for drug resistance based on experience with INH in tuberculosis Not clear if new compounds overcome liver toxicities associated with INH
Fatty acid biosynthesis: FAS I				
Relevant neglected tropical diseases: Tuberculosis (PZA on market; PZA analogs, discovery)	Based on well-established existing drug for tuberculosis treatment	Early stage, so potential improvements over PZA unclear Mammalian cells also have FAS I raising concerns about host toxicity	Addition of new products to drug combinations	Many more advanced programs for tuberculosis drug development that are likely to be approved before this product

Numerous lipid biosynthetic pathway enzymes have been genetically or chemically validated as potential therapeutic targets for neglected tropical diseases. These validated targets represent the best opportunity for immediate screening of existing small molecule libraries from non-neglected tropical disease lipid biosynthesis drug discovery programs.

Neglected Tropical Disease	Fatty Acids	Triglycerides and Phospholipids	Sterols: Mevalonate pathway	Sterols: Isoprenoid pathway	Sterols: Downstream of isoprenoid
Chagas[1,2]	Kinetoplast novel pathway (FAS II-like): endoplasmic reticulum-based elongases (ELOs) for de novo synthesis FAS II in mitochondrion		HMG-CoA (preliminary evidence using on market statins)	Tc Farnysyl pyrophosphate synthase (TcFPPS)	CYP51 Squalene synthase (SQS) Sterol methyl transferase (SMT)
HAT[1,2,3]	Kinetoplast novel pathway (FAS II-like): endoplasmic reticulum-based elongases (ELOs) for de novo synthesis FAS II in mitochondrion			FPPS inhibitors have effects on replication, but target not confirmed Tb protein farnesyl transferase (TbPFT)	CYP51 (not proven in vivo – can salvage cholesterol)

Leishmaniasis[1,2]	Kinetoplast novel pathway (FAS II-like): endoplasmic reticulum-based elongases (ELOs) for de novo synthesis FAS II in mitochondrion			LmFPPS	Lanosterol demethylase
Malaria[1,2,3,4,5]	FAS II in apicomplast organelle: PfENR, PfKASI/II, PfHAD	Phosphatidylcholine synthesis	Unique mevalonate-independent pathway upstream pre-isoprenoid: PfDOXP	FPPS inhibitors have effects on replication, but target not confirmed PfPFT	
Tuberculosis[6]	FAS II (InhA) and FAS I				CYP51 (non-essential) in combination with CYP121

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References

1. Goodman CD and McFadden GI (2008) “Fatty acid synthesis in protozoan parasites: unusual pathways and novel drug targets.” *Current Pharmaceutical Design* **14**: 901-916.
2. Martin MB et al. (2001) “Bisphosphonates Inhibit the Growth of Trypanosoma brucei, Trypanosoma cruzi, Leishmania donovani, Toxoplasma gondii, and Plasmodium falciparum: A Potential Route to Chemotherapy.” *Journal of Medicinal Chemistry* **44**: 909-916.
3. Buckner FS et al. (2005) “Protein farnesyl transferase inhibitors for the treatment of malaria and African trypanosomiasis.” *Current Opinion in Investigational Drugs* **6**: 791-797.
4. Wengelnik K et al. (2002) “A Class of Potent Antimalarials and Their Specific Accumulation in Infected Erythrocytes.” *Science* **295**: 1311-1314.
5. Seeber F (2003) “Biosynthetic pathways of plastid-derived organelles as potential drug targets against parasitic Apicomplexa.” *Current Drug Targets – Immune, Endocrine, & Metabolic Disorders* **3**: 99-109.
6. Schroeder EK et al. (2002) “Drugs that inhibit mycolic acid biosynthesis in Mycobacterium tuberculosis.” *Current Pharmaceutical Biotechnology* **3**: 197-225.

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Tools

Get Involved

Databases/Resources

The Lipidomics Gateway is a free website for researchers interested in lipid pathways and biology run by the LIPID Metabolites and Pathways Strategy (LIPID MAPS) consortium. The website also details protocols for common assays and other analysis common in lipid research

Assays

There are numerous assays available to monitor lipid biosynthesis, including:

- (3H) acetic acid labeling of cultured cells to monitor cholesterol biosynthesis. Following the labeling, lipids are extracted with methanol and chloroform, separated using thin layer chromatography and the cholesterol band is measured by liquid-scintillation counting. More information available here.
- A high throughput assay that identifies inhibitors simultaneously against multiple targets within the FASII pathway of most bacterial pathogens. Merck & Co. developed an assay that measures the incorporation of (14C) malonyl-CoA into long hydrophobic acyl chains of acyl-ACP using partially purified bacterial enzymes of the FAS II pathway. A protocol for this assay is available here.
- Several assays for high-throughput screening of neutral lipid biosynthesis. These assays include biochemical scintillation proximity assays, cell-based lipotoxicity assays, and cell-based in situ fluorescent quantification assays. For a review of these techniques please refer to the recent review by Siloto and Weselake available here.

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Product Details

E1224

Synonyms:
E1224
Ravuconazole pro-drug

Disease:
Chagas disease

Specific Indication:

Product Type:
Drug

PRV Eligible?
No

Target/Technology:
Lipid biosynthesis

Mechanism of Action:
CYP51 (sterol 14 alpha-demethylase) inhibitor

Molecule Class:
Azole

Administration Route:

Notes:

Clinical Trials:

Publications:

FAS 20013

Synonyms:
FAS 20013

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Eligible?
Yes

Target/Technology:
Lipid biosynthesis

Mechanism of Action:
Fatty acid biosythesis

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

InhA inhibitors

Synonyms:
InhA inhibitors

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Eligible?
Yes

Target/Technology:
Lipid biosynthesis

Mechanism of Action:
InhA inhibitor

Molecule Class:

Administration Route:

Notes:

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

Clinical Trials:

Publications:

Lanosterol demethylase inhibitors

Synonyms:
Lanosterol demethylase inhibitors

Disease:
Leishmaniasis

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Lipid biosynthesis

Mechanism of Action:
Lanosterol demethylase inhibitors

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

ND701

Synonyms:
ND701

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Lipid biosynthesis

Mechanism of Action:
Binds to P450 enzymes (potentially CYP51 and CYP121)

Molecule Class:
Azole

Administration Route:

Notes:

Clinical Trials:

Publications:

Posaconazole

Synonyms:
Posaconazole

Disease:
Chagas disease

Specific Indication:

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Lipid biosynthesis

Mechanism of Action:
CYP51 (sterol 14 alpha-demethylase) inhibitor

Molecule Class:
Azole

Administration Route:
Oral

Notes:

FDA approved as an anti-fungal.

Clinical Trials:

NCT01162967

Publications:

20386598

Pyrazinamide analogs

Synonyms:
Pyrazinamide analogs

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Lipid biosynthesis

Mechanism of Action:
FASI inhibitor

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

Sudoterb

Synonyms:
Sudoterb
LL 3858

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Lipid biosynthesis

Mechanism of Action:
INH analog

Molecule Class:
Pyrroles

Administration Route:

Notes:

Clinical Trials:

Publications:

TAK-187

Synonyms:
TAK-187

Disease:
Chagas disease

Specific Indication:

Product Type:
Drug

PRV Elegible?
No

Target/Technology:
Lipid biosynthesis

Mechanism of Action:
CYP51 (sterol 14 alpha-demethylase) inhibitor

Molecule Class:
Azole

Administration Route:

Notes:

Clinical Trials:

Publications: