Background

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What is Energy Metabolism?

Adenosine-5'-triphosphate (ATP) is the main source of energy for all cellular processes. The processes by which ATP is produced or used up are also referred to as energy metabolism.

Overview

Adenosine-5'-triphosphate (ATP) is produced by the breakdown of biological macromolecules, such as sugars, proteins, and lipids. As these macromolecules are broken down, electrons are released. The electrons are funneled into electron acceptors and passed through a series of membrane-associated electron carriers, known as the electron transport chain. The electron transport chain generates a proton gradient whereby the concentration of protons on one side of the membrane is higher than the other. As protons move back across the membrane towards the direction with lower concentration through a channel, they drive an enzyme known as ATP synthase to produce ATP from its precursor adenosine-5'-diphosphate (ADP). Production of ATP occurs primarily in the membrane of mitochondria of eukaryotic cells or the plasma membrane of bacteria.

Interruption of electron transport or ATP synthase can block the production of ATP and result in lethal effects. For instance, the poison cyanide inhibits the electron transport chain by binding to cytochrome oxidase, an essential electron carrier in the chain. Mutations in ATP synthase are associated with several neurodegenerative diseases in humans.[1] It may be possible to exploit differences in the electron transport chain carriers or synthetic enzymes using in ATP production in human cells, bacteria, and some eukaryotic parasites to develop novel therapeutics.

Biosynthetic pathways use ATP to produce new biological macromolecules. The drug target potential of enzymes that use ATP to produce new biological macromolecules is discussed in other drug target profiles (see lipid biosynthesis, nucleic acid synthesis, and protein synthesis).

Existing Products

Because energy metabolism, especially ATP production, is essential for all life, it is theoretically a powerful therapeutic target for a wide range of organisms and diseases. However, the risk for toxic side effects when targeting energy metabolism pathways must also be considered. Exploitation of differences in energy metabolism between human cells, bacteria, and some parasitic organisms is an area of interest for neglected disease therapeutics as this approach has the potential to produce potent new therapeutics with minimal side effects.

Energy Metabolism Inhibitors as Non-Neglected Tropical Disease Therapeutics

There are no energy metabolism inhibitors in use in humans that target the electron transport chain or ATP synthase for non-neglected disease indications. However, there are numerous known inhibitors of electron transport and ATP synthase in the scientific literature that may serve as a starting point for future drug development.[1]

Energy Metabolism Inhibitors as Neglected Tropical Disease Therapeutics

The cytochrome bc(1) complex of Plasmodium falciparum, a key carrier in the electron transport chain, is the target of the antimalarial

drug atovaquone.[2] This is the only on market product targeting the electron transport chain, but it has not been used widely to treat malaria due to the rapid emergence of drug resistance to this product after introduction. However, atovaquone demonstrates that selective targeting of components of the electron transport chain is possible and may be worth exploring for other neglected diseases.

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References

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2. Barton V et al. (2010) “Inhibiting Plasmodium cytochrome bc1: a complex issue.” *Current Opinion in Chemical Biology* **14**: 440-446. PMID: 20570550

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Pipeline & Analysis

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PIPELINE

Product/Research Program	Developers	Discovery	Pre-clinical	Phase I	Phase II	Phase III
TMC207	Global Alliance for TB Drug Development Tibotec					
Diarylquinolines	Global Alliance for TB Drug Development Tibotec University of Auckland					
Energy metabolism inhibitors	AstraZeneca Global Alliance for TB Drug Development University of Pennsylvania					
GSK 932121	GlaxoSmithKline			On Hold		
MK 4815	Medicines for Malaria Venture Merck & Co., Inc.		On Hold			
GSK 2243979A and GSK 2223413A	GlaxoSmithKline Medicines for Malaria Venture	On Hold				

ANALYSIS

Novel therapeutics in development targeting energy metabolism pathways are currently limited to:

- Tuberculosis ATP synthase
- Malaria electron transport chain

The relative strengths, weaknesses, opportunities and risks for energy metabolism inhibitors that are currently in development for neglected diseases are summarized here.

	Strengths	Weaknesses	Opportunities	Risks
ATP synthase inhibitors				
Relevant neglected tropical diseases: Tuberculosis (TMC207, phase II; diarylquinolines – TMC207 backup, discovery; AstraZeneca energy metabolism inhibitors, discovery)	Effective against MDR-TB in phase II clinical trial with minimal adverse events1,2 Novel mechanism relative to approved tuberculosis drugs so likely to be effective against multi-drug resistant organisms		Combination with existing or novel tuberculosis drugs with other mechanisms of action Application to other mycobacterial infections (e.g. Buruli ulcer and leprosy)	Inhibition of ATP synthase in mammalian cells is toxic which may increase the risk for side effects, however no safety issues have been reported thus far in clinical trials
Electron transport chain inhibitors				
Relevant neglected	GSK932121 is selective	All programs for this	Electron transport chain	Inhibition of electron

tropical diseases: Malaria (atovaquone, on market; GSK932121 and MK4815, on hold)	for *P. falciparum*[3] cytochrome bc1 Based on proven mechanism of action (atovaquone)	target are currently on hold Introduction of atovaquone resulted in rapid emergence of drug resistance	is essential for all organisms, so it may be possible to identify selective inhibitors of electron carriers for other neglected diseases	transport in humans is known to be lethal creating a high risk for negative side effects Potential for drug resistance may be higher than other mechanisms of action

Prediction and validation of energy metabolism related targets is still ongoing for neglected diseases. Furthermore, validation of the ability to selectively inhibit these targets over related targets in humans is essential. Predicted and validated targets for neglected diseases related to ATP production are summarized below.

Neglected Tropical Disease	Potential Targets
Tuberculosis[4-6]	ATP synthase, electron transport chain carriers, NADH dehydrogenase (NDH2), multiple predicted targets
Malaria[7]	Type II NADH:quinone oxidoreductase (PfNDH2), succinate dehydrogenase (SDH), cytochrome bc1
Kinetoplasts: Leishmaniasis, Chagas disease, HAT[8-9]	Cytochrome c reductase (respiratory complex III), glycosomes

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References

1. Rustomjee R, Diacon AH, Allen J *et al.*: Early bactericidal activity and pharmacokinetics of the dairylquinoline TMC207 in treatment of pulmonary tuberculosis. *Antimicrob. Agents Chemother.* **52**, 2831–2835 (2008).
2. Diacon AH, Pym AP, Grobush M *et al.*: The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N. Engl. J. Med.* 360, 2397–2405 (2009).
3. Jimenez-Diaz MB et al. (2009) “Improved murine model of malaria using Plasmodium falciparum competent strains and non-myelodepleted NOD-scid IL2Rgammanull mice engrafted with human erythrocytes.” Antimicrob Agents Chemother **53**: 4533-4536.
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6. Anishetty S et al. (2005) “Potential drug targets in Mycobacterium tuberculosis through metabolic pathway analysis.” Comput Biol Chem **29**: 368-378.
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9. Michels PA et al. (2006) “Metabolic functions of glycosomes in trypanosomatids.” Biochim Biophys Acta **1763**: 1463-1477. PMID: 17023066

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Tools

Get Involved

Databases/Resources

More information on energy metabolism pathways, mitochondria, and ATP production can be found at:

- KEGG PATHWAY Database
- The Mitochondrion
- Metabolic Poisons

Assays

Inhibition of energy metabolism is generally measured by changes in ATP production upon treatment of whole cells or biochemically isolated mitochondria. Numerous standard assays are available including:

- Promega CellTiter-Glo® Assay
- Sigma-Aldrich ATP Assays

Standard protocols and well characterized inhibitors are also available to study ATP synthase:

- Lab protocols useful for ATP synthase studies
- Review of known ATP synthase inhibitors

The majority of these assays have been adapted to high throughput formats.

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Product Details

Diarylquinolines

Synonyms:
Diarylquinolines

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Energy metabolism

Mechanism of Action:
Adenosine triphosphate (ATP) synthase enzyme inhibitor

Molecule Class:
Diarylquinoline

Administration Route:

Notes:

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

Clinical Trials:

Publications:

Energy metabolism inhibitors

Synonyms:
Energy metabolism inhibitors

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Energy metabolism

Mechanism of Action:
Energy metabolism inhibitors

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

GSK 2243979A and GSK 2223413A

Synonyms:
GSK 2243979A and GSK 2223413A
Backup program: 4-pyridone

Disease:
Malaria

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Energy metabolism

Mechanism of Action:
Inhibits electron transport chain in the mitochondrion

Molecule Class:
4-pyridone

Administration Route:

Notes:

Clinical Trials:

Publications:

GSK 932121

Synonyms:
GSK 932121
4-pyridone class inhibitors

Disease:
Malaria

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Energy metabolism

Mechanism of Action:
Inhibits electron transport chain in the mitochondrion

Molecule Class:
4-pyridone

Administration Route:

Notes:

Clinical Trials:

NCT00811356

Publications:

19596869

MK 4815

Synonyms:
MK 4815

Disease:
Malaria

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Energy metabolism

Mechanism of Action:
Inhibits electron transport chain in the mitochondrion

Molecule Class:

Administration Route:

Notes:

Clinical Trials:

Publications:

TMC207

Synonyms:
TMC207
R207910

Disease:
Tuberculosis (TB)

Specific Indication:

Product Type:
Drug

PRV Elegible?
Yes

Target/Technology:
Energy metabolism

Mechanism of Action:
Adenosine triphosphate (ATP) synthase enzyme inhibitor

Molecule Class:
Diarylquinoline

Administration Route:
Oral

Notes:

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

Clinical Trials:

NCT00946842
NCT00910871
NCT01012284

Publications:

15591164
19494215

NCT00449644
NCT00523926
NCT01215851
NCT01215110