Mitochondrial Toxicity in Drug Discovery

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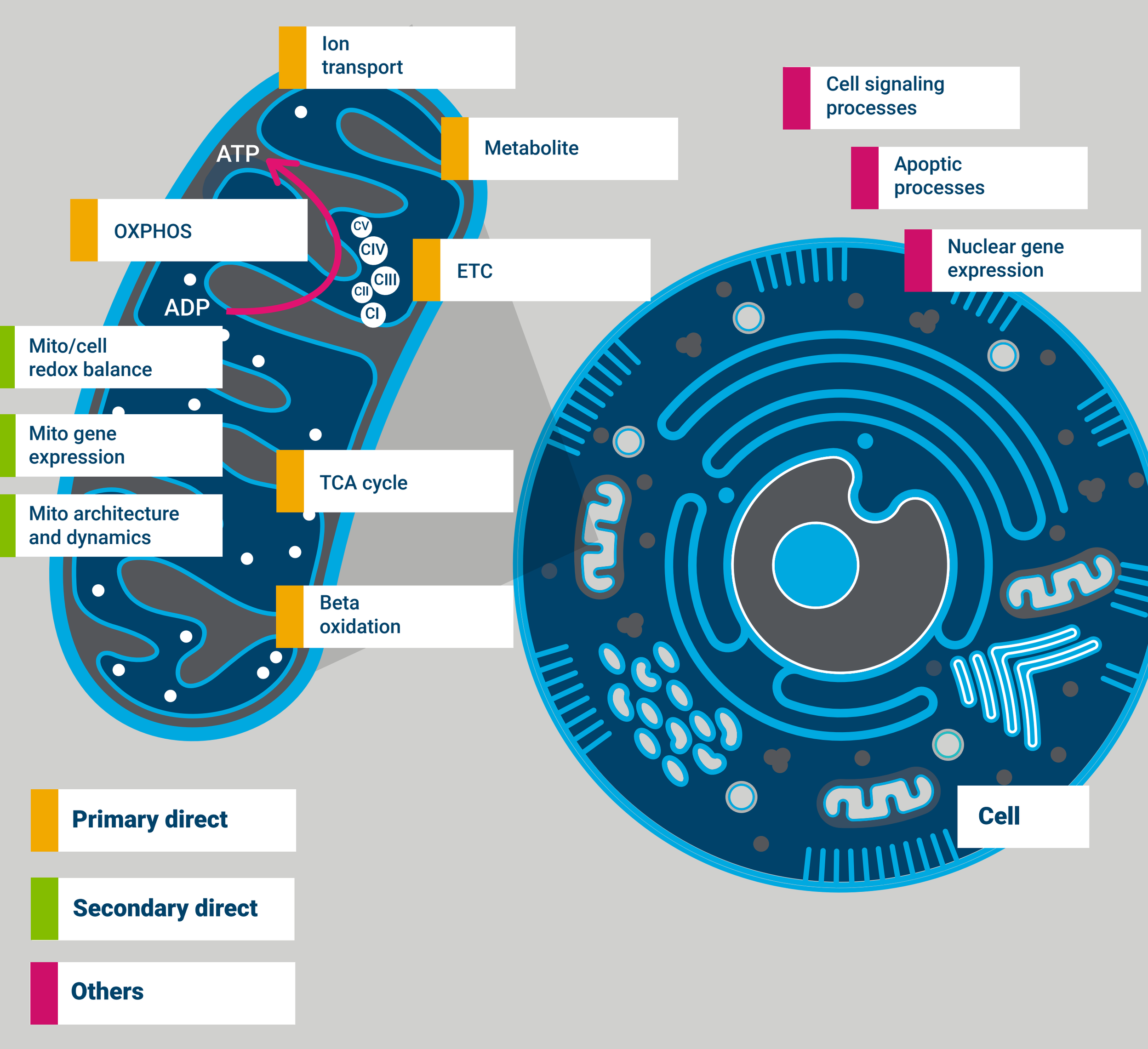
Mitochondria are critical regulators of normal cell function and health; consequently, their dysfunction plays a central role in many diseases.[1] Drug-induced mitochondrial dysfunction has been linked to compound attrition, organ toxicity, black-box warnings, and market withdrawals, therefore it is important to identify mitochondrial toxicity during the early stages of the drug discovery process.

Although end-point assays are the most common methods used, they are not sensitive enough to capture all compounds with mitochondrial toxicity, leading to late-stage failures. New *in vitro* strategies are being introduced to the market, which are more specific and sensitive. This infographic will explore the impact of mitochondrial toxicity and highlight the benefits of novel *in vitro* strategies for drug safety.

Why is mitochondrial toxicity important in drug discovery?

Mitochondria play a pivotal role in cellular energy (ATP) production and the maintenance of homeostasis. As a result, the mitochondrial network is widely regarded as an important site for the off-target side effects of therapeutics. The schematic below shows the key mitochondrial pathways and processes that may be potential targets of drug-induced mitochondrial toxicity.



Drug-induced mitochondrial toxicity is responsible for many organ-related toxicities, such as:[2]

Hepatotoxicity | Cardiotoxicity | Neurotoxicity | Nephrotoxicity

Since the late 1990s, the US Food and Drug Administration has withdrawn dozens of drugs from the market due to adverse effects that have been linked to mitochondrial dysfunction. Here are a few examples:[2,3]

- In 2000, **Troglitazone** – an antidiabetic drug – was withdrawn due to off-target effects on the mitochondrial electron transport chain, causing hepatotoxicity.[4]
- In 2001, **Cerivastatin** – a lipid-lowering drug – was withdrawn due to mitochondrial toxicity that affected complex III-related respiration, causing rhabdomyolysis.[2]
- In 2006, **Zalcitabine** – an antiretroviral drug for HIV treatment – was withdrawn due to associated mitochondrial toxicity.[3]

The implication of mitochondrial toxicity in the etiology of many diseases (e.g., cancer, diabetes, cardiovascular disease, and neurodegeneration) is driving the development of methods that enable more direct interrogations of mitochondrial function.[2]

De-risking the drug discovery pipeline

Mitochondrial toxicity studies can be implemented in any part of the workflow to de-risk the drug discovery pipeline and ensure consumer safety.

1

Screening

Discovery toxicology is the first step to uncover compounds with potential mitochondrial toxicity in the compound library.

2

Investigative

In investigative toxicology, the severity and mode of action is assessed, and preclinical risk factors are identified. This is done by analyzing the magnitude and type of mitochondrial toxicity.

3

Mechanistic

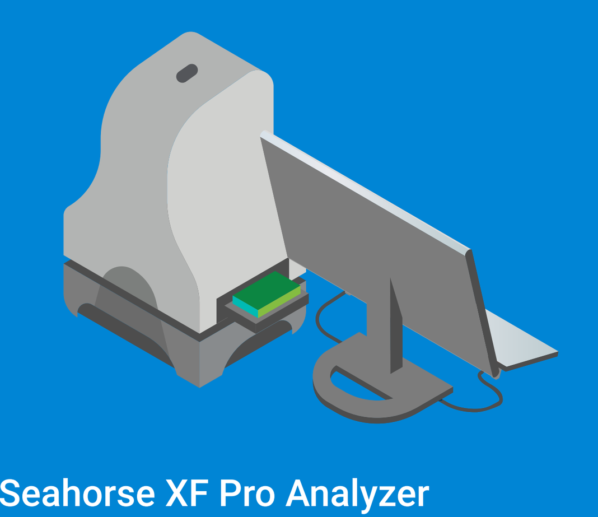
Mechanistic mitochondrial toxicity studies investigate how the compounds disrupt mitochondrial function. This information helps to discover the link between observed toxicity and mechanism of action.

How do we investigate mitochondrial toxicity?

Scientists have explored several ways to assess mito tox, which include measuring oxygen consumption, mitochondrial membrane potential (MMP), or total ATP in cells cultured in the presence of a galactose – this is called a glu/gal method. Oxygen consumption assays based on live cell bioenergetic measurements are considered the most informative, sensitive, and specific methods, as they provide direct measurements of mitochondrial (dys)function.[5,6] However, historically the absence of a standard testing protocol and/or data analysis tools, has limited the wide adoption of these assays. The new end-to-end Seahorse XF solution now provides improved usability and data consistency.

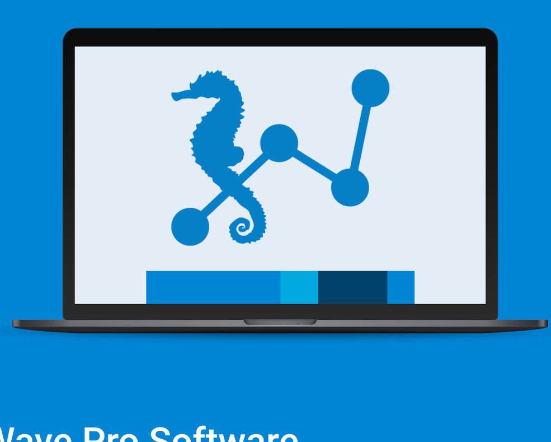
A new end-to-end Agilent Seahorse XF solution with improved usability and data consistency

Built on oxygen consumption measurements, the Agilent Seahorse XF mito tox solution integrates the new Agilent Seahorse XF Pro analyzer, enhanced software features, and consumables to deliver an Agilent workflow for assessing mitochondrial function with high specificity and sensitivity. From assay design to data quality assessment and interpretation, the Agilent solution will enhance the entire XF assay experience, improving toxicity predictions and de-risking your drug pipeline for greater success.



Seahorse XF Pro Analyzer

- ✓ Enhance the sensitivity and precision of oxygen consumption measurements
- ✓ Deliver better well-to-well data consistency



Wave Pro Software

- ✓ Improve the process of creating assay templates and protocols
- ✓ Ensure data confidence with data quality analysis view to automatically examine the quality of your assay files in every well

Seahorse XF Cell Mito Tox Assay kit

- ✓ Provide validated reagents with standardized and streamlined workflow
- ✓ Offer simplified assay design and relevant mito tox parameters for easily identifying the type and magnitude of mitochondrial toxicity

Seahorse Analytics

- ✓ Simplify data processing and transform raw data into standardized mito tox parameters using dedicated analysis companion views
- ✓ Deliver actionable results in organized and shareable summary reports

Click here to find out more information about Agilent mito tox solutions

References:

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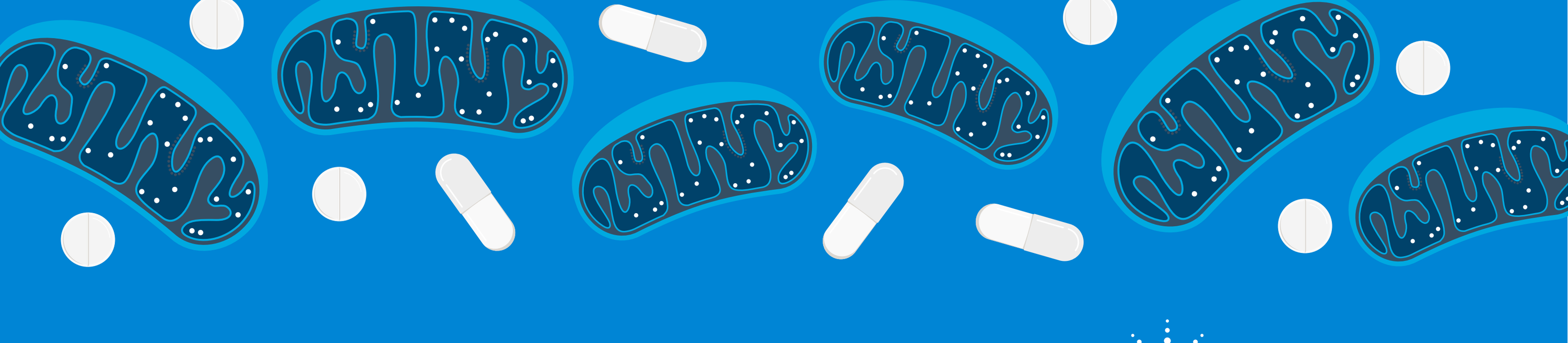

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