

Mitochondrial Substrate Invention Ltd

Company Presentation



Focus on:

- Advancing of IP protected compounds
 - that address the biggest challenge of the aging world;
 - have uniquely short route/time to market
- Cost control and lean operations
- Developing novel product with exclusive delivery route for pharmaceutical application
- Generating extraordinary profits



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Mitochondrial Substrate Invention (MSI) Ltd
UK Registered Company 09051662

What is MSI?



1

MSI

MSI Ltd is UK registered private company.
It was set up to enable global IP exploitation of the small molecule.
The composition is unique combination of two known ingredients. Three owners/ partners and co-inventors.

2

MSI Mission

To develop functional products directed to sustain healthy ageing in the modern world.

1. Pharmaceutical product - Intranasal Insulin/Mitochondoline nasal spray based on the synergy of action.
2. Food supplementation product with the cognitive health structure/functional claim

3

Aim of the presentation

Mitochondoline® is a small molecule and has been selected as best candidate for sensitizing brain insulin receptors for the insulin action.

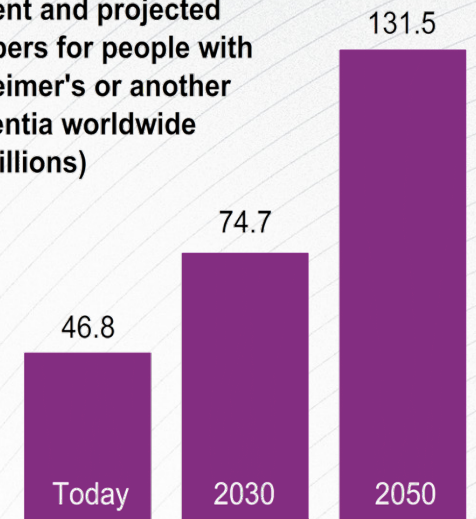
The mechanism of action through mitochondrial signalling pathway is the novel discovery.

Alzheimer's disease (AD) and other dementias are the greatest challenges of the modern world. AD is conceptualised as Type 3 Diabetes.



Today one in six people are aged 65 or over.
In just thirty years it will be more than one in four.
Six drugs have been approved by FDA to treat AD symptoms.
None of the drugs slows or stops neurodegeneration.

Current and projected
numbers for people with
Alzheimer's or another
dementia worldwide
(in millions)



Source: *World Alzheimer's Report 2015*. The Global Impact of Dementia.
An analysis of prevalence, incidence, cost and trends. Published by:
Alzheimer's Disease International (ADI), London.



For far too long dementia condition has been ignored, down-played or mistaken as a natural part of the ageing process. The truth is that dementia now stands alongside cancer as one of the greatest enemies of humanity. It's time for a global fight-back against dementia



-David Cameron in "Global Dementia Legacy Event" -

Mitocholine®. Novel biology, novel target: first in class neuronal insulin receptor sensitizer

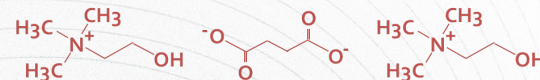
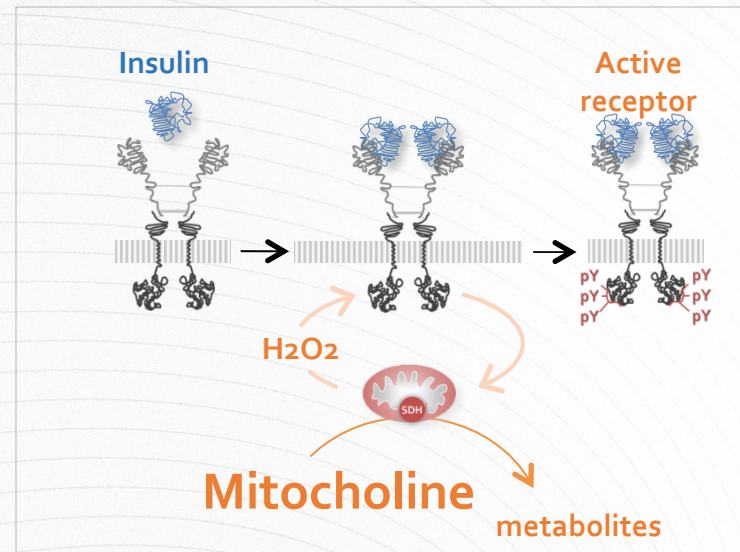


Targeting brain insulin receptors is our approach for the treatment of CNS disorders such as AD, dementia, cognitive decline, major depression, and anxiety.

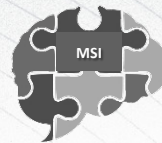
The novel pathway of neuronal insulin receptor activation is through mitochondrial release of H_2O_2 which serves as all-or-nothing condition for insulin receptor activation in response to insulin.

No activation of insulin receptor occurs, even at the highest insulin dose, if the H_2O_2 signal does not exceed a certain threshold.

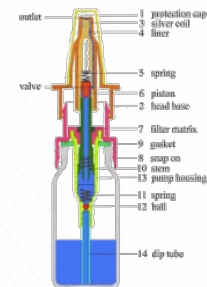
Our discovery of this mitochondrial signaling pathway changes the classic view on how insulin receptor is activated in neurons.



Mitocholine: Active Pharmaceutical Ingredient & drug product



Description		
Formula	C ₁₄ H ₃₂ N ₂ O ₆ MW 324.41 g/mol	
Names	Dicholine salt of succinic acid, Dicholine succinate, DISU	
Manufacturing process	cGMP synthesis:	2Choline base + Succinic acid → (Choline) ₂ succinate + H ₂ O
API	50% DISU water solution cGMP API	DSM ResCom Pharma Chemicals Regensburg GmbH, Germany
Stability	Stable for 3 years at 25°C without decomposition	HWI Analytik Pharma Solutions GmbH Germany
Analytical testing	Has been developed	HWI Analytik Pharma Solutions GmbH Germany
Drug product	Nasal spray 7% DISU (preservatives-free)	Ursapharm Arzneimittel GmbH, Germany
Dossier	Investigational Medical Product Dossier for DISU chemistry, manufacturing, and controls information has been prepared	Rapid Pharma Development GmbH Switzerland



Proof of concept: Intranasal Mitocholine against β -amyloid-induced amnesia

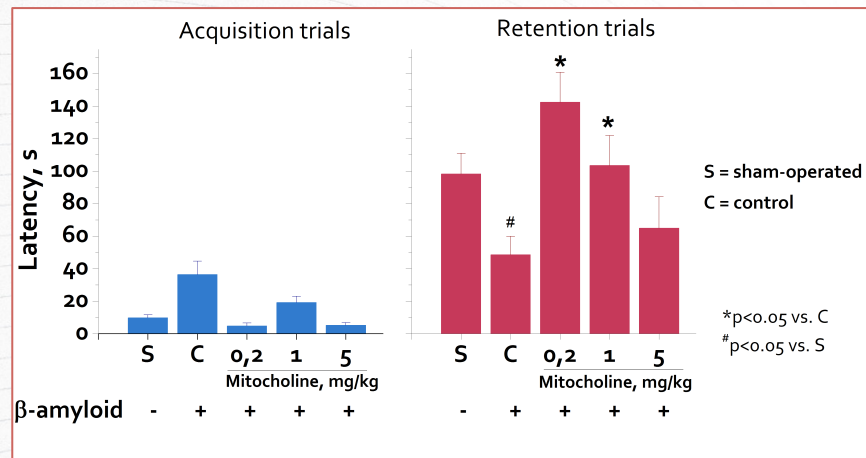


Amnesia was induced by a single injection of β -amyloid peptide(25-35) into nucleus basalis magnocellularis (NBM) of rat brains, as described in Storozheva et al, *BMC Pharmacol*, 2008, 8:1. Then, rats were treated intranasally with Mitocholine® doses of 0.2, 1, and 5 mg/kg for 7 days. Passive avoidance test was performed to assess Mitocholine® effects on memory.

Illustration shows that intranasal Mitocholine® significantly ameliorated β -amyloid-induced amnesia at doses 0.2 and 1 mg/kg, while was ineffective at dose 5 mg/kg (bell-shaped dose-response).

Mitocholine® is effective via intranasal administration for memory enhancement and can be used in combination with intranasal insulin for treating AD and other dementias.

Effect of intranasal Mitocholine on performance in Passive Avoidance Test (learning and memory) in the model of β -amyloid toxicity



This figure was made based on unpublished data.

Light water: adjunctive ingredient to Insulin/ Mitocholine® nasal spray



Although water is considered to be an individual substance H_2O , this view is oversimplified and natural water consists of light and heavy water molecules, with a predominance of the light ones.

For the illustration, ocean water consists of:

- 99.73% of the light water molecule ($H_2^{16}O$)
- 0.27% of the heavy water molecules

Conventionally, a level of heavy molecules is measured as heavy-to-light hydrogen (D/H) ratio and expressed in parts-per-million (ppm).

Natural waters may vary by 50% in their levels of heavy molecules, from 89 parts-per-million in Antarctica (lightest water) to 175 parts-per-million in the internal pools of arid zones (heaviest water).

As used herein, the term “Light Water” refers to any water having less than 140 ppm of heavy molecules. Our novel intranasal formulation of Insulin / Mitocholine® is based of the light pharmaceutical water.

H ₂ O		%	Mass
	H ₂ ¹⁶ O	99.73	18
	H ¹⁶ OD	0.031	19
	H ₂ ¹⁷ O	0.037	19
	H ₂ ¹⁸ O	0.200	19
	H ¹⁷ OD	0.00001	20
	H ¹⁸ OD	0.00006	20
	D ₂ ¹⁶ O	0.0005	20
	D ₂ ¹⁷ O	ND	21
	D ₂ ¹⁸ O	ND	21
		100 %	

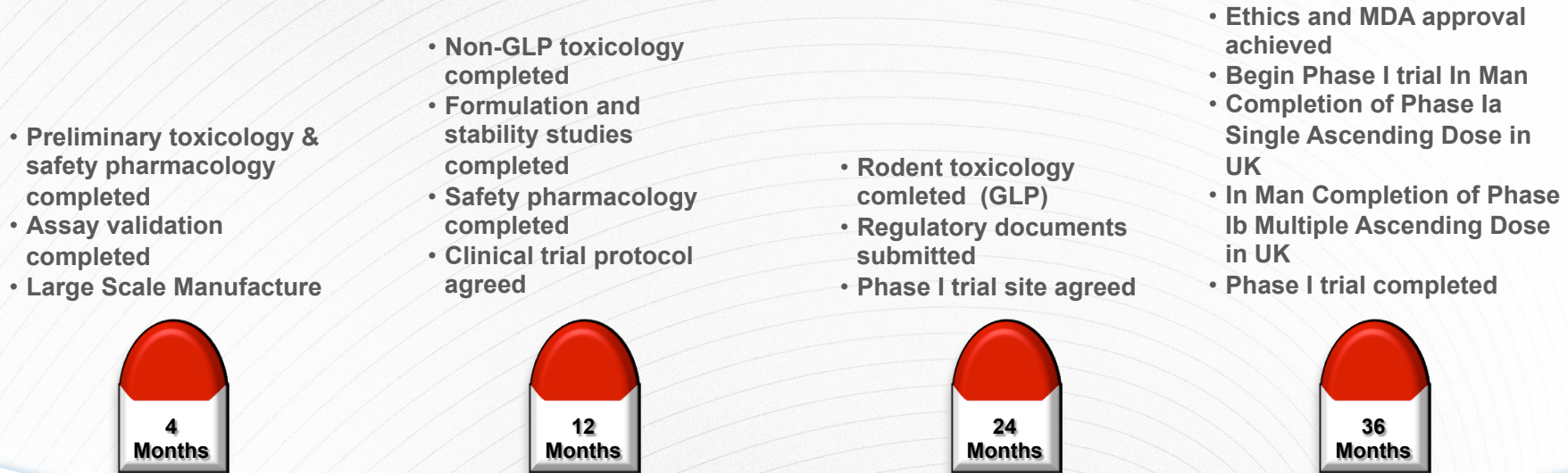
Proposed Milestones /time frame and risks for the development of the Insulin/Mitocholine light water nasal spray



The usual toxicity risks are non-existent due to the fact that Mitocholine® is the combination of two safe proofed human metabolites.

The effectiveness is confirmed by the recent clinical trials of the nasal insulin.

We aim at confirming superior effect to insulin alone due to the additional receptor sensitization.



Food supplementation. Second product with the cognitive health structure/ functional claim. Mitocholine® plus Light Water



Mitocholine® proposed to be developed as soft drink is a proprietary composition with unique mechanism of action: it helps endogenous insulin to activate brain insulin receptors to preserve cognitive ability in persons at risk of AD and other dementias.

Mitocholine® to be used in the soft drink in amounts, which meet requirements of regulation with respect to choline and succinate.

Note: Mitocholine® in amounts of 250 or 500 mg per serving is an excellent source of choline, an essential nutrient, according to FDA labelling rules: <http://digital.bnppmedia.com/article/Choline%3A+The+Silent+Deficiency/1896889/0/article.html>

Rationale for use of about 125 ppm deuterium content (light water) water in MSI's soft drink:

- Efficacy. "125 ppm water" could provide benefit for health in older adults (45+).
- Cost efficiency. "125 ppm water" is still cheap enough for manufacturing on a big scale.
- Authenticity. "125 ppm water" is an excellent protective marker for authentic product.
- IP protection and technical know how

Light Water patent position:



Patent No	Title	Status	Expiry date
RU 2482706	Medical food for dietary management of depression & anxiety and methods	Granted	2031-12-05
	US20130142883	US 9,220,727	Granted
	<i>Divisional applications</i>		
		US20150024062	application
		US20150064277	application
		US20150064276	application
	WO2013085431	application	2031-12-05
	EP2787842	application	2031-12-05
	CA2858192	application	2031-12-05
	AU2012348397	application	2031-12-05
	CN103987281	application	2031-12-05
	JP2015500832	application	2031-12-05
	KR20140103289	application	2031-12-05
RU 2481009	Food for the dietary management of depression and anxiety	Granted	2031-12-05

Mitocholine® patent position:



Patent No	Title	Status	Expiry date
US 7,666,908	Method for enhancing cognitive function	Granted	2025-03-04
JP 3944393	Synergistic compositions containing choline base and succinic acid for treating insulin resistance and diabetes	Granted	2020-04-10
PCT/RU2008/000720	Choline salts of succinic acid for the treatment of depression, anxiety, schizophrenia, sleep disorder, and epilepsy		
	WO2010062206		
	US 8,673,977	Granted	2028-11-26
	JP 5408261	Granted	2028-11-26
	CN 102223883	Granted	2028-11-26
	KR 10-1360569	Granted	2028-11-26
	EP 2349246 A1	Pre-grant	2028-11-26
PCT/GB2015/051898	Nutrient solution for enhancement of cognitive function	Application*	2034-06-30

*Written opinion of the international searching authority: claims covering combination of Mitocholine and light water are patentable