Date: 6 November 2017 **Sydney, Australia**

ASX: NOX

Noxopharm Limited

ABN 50 608 966 123

Registered Office:
Suite 1 Level 6
50 Queen St
Melbourne VIC 3000
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Operational Office:
Suite 3, Level 4
828 Pacific Highway
Gordon NSW 2072
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Mr Peter Marks
Chairman
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Dr Graham Kelly
Chief Executive Officer
Managing Director

Dr Ian Dixon
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ASX Limited
20 Bridge Street
SYDNEY NSW 2000

EGM presentations

- **NYX-104. Professor Gary Housley**
- **NYX-205. Dr Benny Evison**
- **NYX-330. Dr Ian Dixon**

Sydney, 6 November 2017: Noxopharm is pleased to release the 3 presentations being made today in conjunction with the Company's Extraordinary General Meeting.

Two transactions are being considered by shareholders which, if approved, will see a subsidiary company, Nyrada Inc, created as a drug development business with a commencing pipeline of 3 drug assets – NYX-104, NYX-205 and NYX-330.

The EGM is being held today (Monday 6 November) at 10 am at the Noxopharm offices: Level 4, Suite 3, 828 Pacific Highway, Gordon.

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About NYX-104
NYX-104 is being developed to assist patient recovery after head and spinal trauma. It is a small molecule kinase-inhibitor that blocks TRPC class ion channel-regulated influx of calcium ions and mobilisation of calcium stores in axons exposed to glutamate overload.

About NYX-205
NYX-205 is being developed as an anti-inflammatory drug to treat inflammatory conditions of the central nervous system (eg. Alzheimer's Disease, multiple sclerosis) and peripheral nerves (peripheral neuropathy), bowel (ulcerative colitis, sclerosing cholangitis) and liver (NASH). It is a small molecule inhibitor of thromboxane synthase.

About NYX-330
NYX-330 is being developed to treat hypercholesterolaemia. It is a small molecule inhibitor of PCSK9.

About Noxopharm
Noxopharm is an Australian drug development company with offices in Sydney and Hong Kong. The Company has a primary focus on the development of drugs to address the problem of chemotherapy- and radiation-resistance in cancer cells, the major hurdle facing improved survival prospects for cancer patients. NOX66 is the first pipeline product, with later generation drug candidates under development. The Company also has initiated a pipeline of non-oncology drugs.

About Nyrada Inc.
Nyrada Inc is a recently formed, New York-based biotechnology company established to house Noxopharm non-oncology drug assets.

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Forward Looking Statements

This announcement may contain forward-looking statements. You can identify these statements by the fact they use words such as “aim”, “anticipate”, “assume”, “believe”, “continue”, “could”, “estimate”, “expect”, “intend”, “may”, “plan”, “predict”, “project”, “plan”, “should”, “target”, “will” or “would” or the negative of such terms or other similar expressions. Forward-looking statements are based on estimates, projections and assumptions made by Noxopharm about circumstances and events that have not yet taken place. Although Noxopharm believes the forward-looking statements to be reasonable, they are not certain. Forward-looking statements involve known and unknown risks, uncertainties and other factors that are in some cases beyond the Company’s control that could cause the actual results, performance or achievements to differ materially from those expressed or implied by the forward-looking statement. No representation, warranty or assurance (express or implied) is given or made by Noxopharm that the forward-looking statements contained in this announcement are accurate and undue reliance should not be placed upon such statements.

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Targeting glutamate-mediated excitotoxicity in the brain using NYX-104

Gary Housley, *Ph.D.*

Translational Neuroscience Facility & Dept. Physiology, School of Medical Sciences, UNSW Sydney

NOXOPHARM

Translational Neuroscience Facility

Industry Partner: Noxopharm Pty Ltd

Brain Sciences UNSW

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J. Parmar

Contributors

Translational Neuroscience Facility
UNSW Sydney
Scientia Prof. Gary Housley
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Ms. Jasneet Parmar
Dr. Chamini Perera
Dr. Georg von Jonqueries

Noxopharm
Dr. Benny Evison
Dr. Graham Kelly

Declaration: Gary Housley is a co-inventor on a patent filed by New South Innovations Pty Ltd (UNSW Sydney) on TRPC ion channels as a therapeutic target for brain injury, and a patent filed by Noxopharm for drug action of NYX-104 in neuroprotection from stroke and related excitotoxic brain injury; Gary Housley holds shares in Noxopharm P/L. Research was funded by a project grant from Noxopharm to UNSW Sydney with Gary Housley as principal investigator.

- Procedures for animal models were approved by the UNSW Sydney Animal Care and Ethics Committee and follow the NHMRC guidelines for use of animals for biomedical research.

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Date 16 March 2017 Sydney, Australia

http://www.asx.com.au/asxpdf/20170316/pdf/43gv3ts2cl36bh.pdf

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Noxopharm and UNSW combine on stroke project

- **Noxopharm drug identified as potential brain/spinal cord injury preventative**
- **First-in-class drug to hasten rehabilitation from brain and spinal cord injury**
- **Made possible because of NOX66 drug delivery platform**
- **UNSW assisting in pre-clinical studies.**

Sydney, 16 March 2017: Noxopharm Ltd (ASX: NOX) today unveils the first of its non-oncology drug pipeline, having entered into a research agreement with the University of New South Wales (UNSW) to develop a unique and highly sought preventative treatment for damage to the central nervous system. This includes stroke and spinal injury, and potentially a wide range of neurodegenerative diseases.

The collaboration brings together key Australian intellectual properties owned by Noxopharm and UNSW that together form the basis for a potential treatment to prevent the debilitating after-effects of brain and spinal cord injury. The ultimate objective is a drug that would be delivered following acute brain or spinal cord injury to prevent further spread of that injury.

The aim of the proposed drug is not to treat the original injury (eg. trauma, stroke etc), which often is limited enogh to self-repair, but to stop the cascade of death of nerve cells (known as *excitotoxicity*) that occurs in the brain and spinal cord after the initial injury and which typically leads to an area of cell death that is too large to be repaired. This 'follow-on damage' typically accounts for most of the loss of function following such injuries. Limiting this 'follow-on damage' is expected to make a significant difference to the recovery prospects of people following brain and spinal cord injury. There currently is no effective treatment of excitotoxicity.

https://www.finnewsnetwork.com.au/CompanyReports/Noxopharm/20170316/Noxopharm-Announces-UNSW-Combine-on-Stroke-Project

https://newsroom.unsw.edu.au/news/health/working-towards-drug-limit-brain-injury

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Translational Neuroscience – identification of NYX-104 as a neuroprotective drug to reduce excitotoxic brain injury

- Identification of a novel Ca^{2+} permeable ion channel (TRPC3) activated by mGluR as a new drug target for reducing the expansion of the penumbra following stroke.
- *In vitro* assays: HEK293 cells (genetically-encoded Ca^{2+} imaging)
- *In vivo*: photothrombotic infarcts; intravital multiphoton imaging

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Epidemiology of Stroke

- Annually, 15 million people worldwide suffer a stroke.
- Stroke is Australia's second single greatest killer after coronary heart disease and a leading cause of disability.
- 65% of stroke survivors suffer a disability which impedes their ability to carry out daily living activities unassisted.
- Stroke kills more women than breast cancer and more men than prostate cancer.
- In 2017 Australia, there will be almost 56,000 new and recurrent strokes – that is one stroke every nine minutes
- In 2017 Australia there will be more than 475,000 people living with the effects of stroke. This is predicted to increase to one million by 2050
- Around 30% of stroke survivors are of working age [under the age of 65]
- The financial cost of stroke in Australia is estimated to be $5 billion each year.

https://strokefoundation.org.au/About-Stroke/Facts-and-figures-about-stroke

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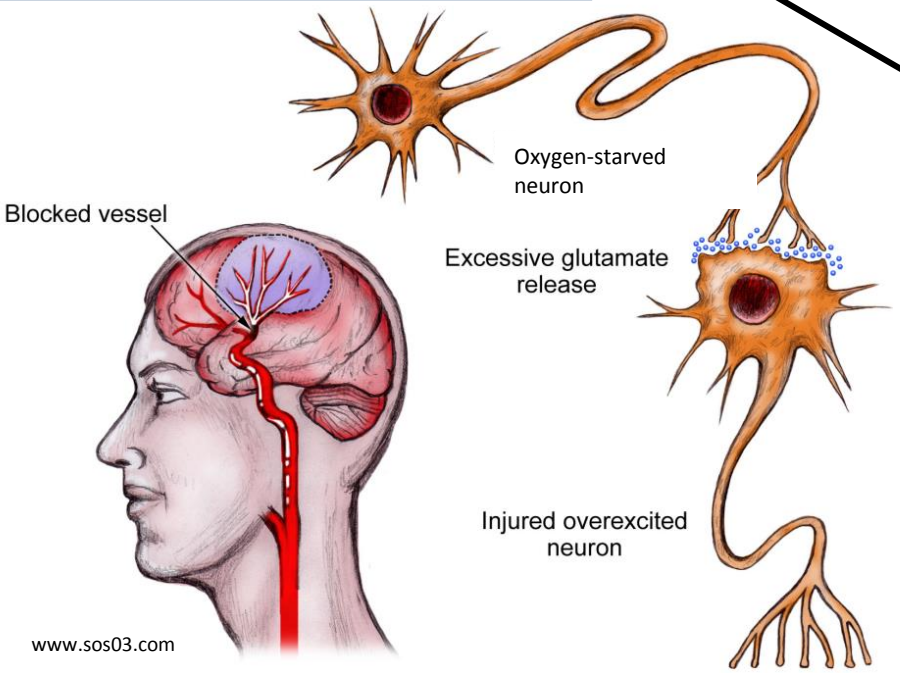
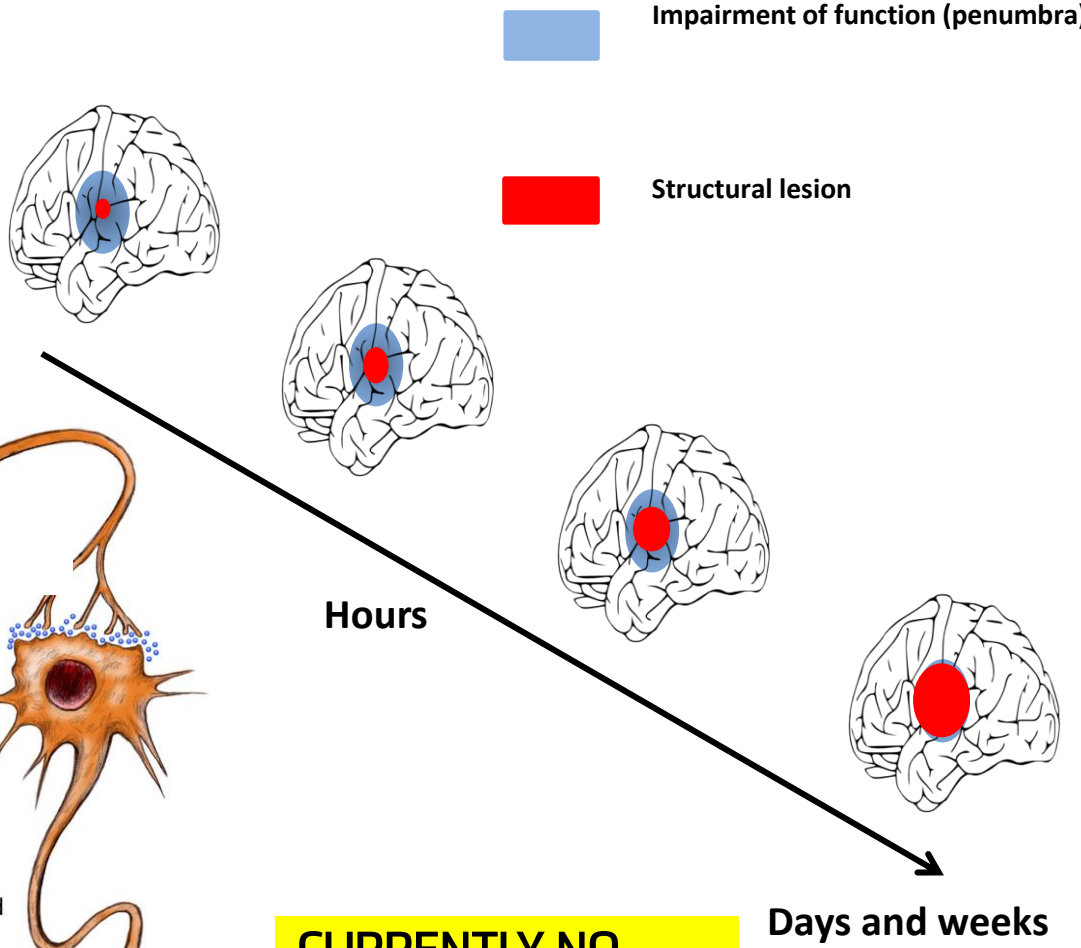
Brain ischemia from stroke and other brain injuries and pathologies causes excess release of the excitatory neurotransmitter – Glutamate – which chronically activates neurons and drives spread of brain injury





CURRENTLY NO NEUROPROTECTIVE TREATMENTS AVAILABLE FOR STROKE

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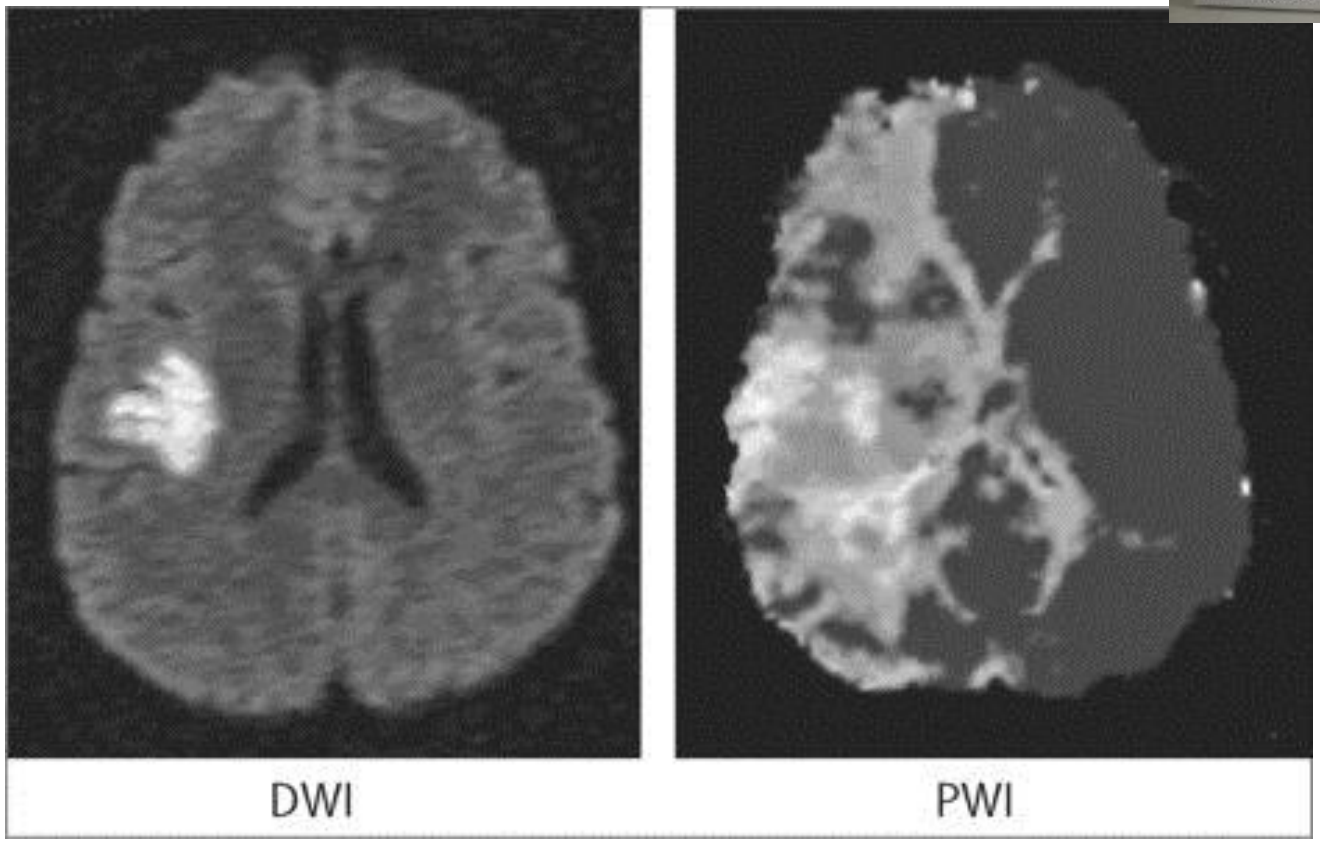
Current treatments for Stroke are directed to re-perfusion and are time-critical

- tPA - thrombolytic agents are the principal recourse for restoring perfusion (< 15% of thrombotic strokes; within 3 hours)
- Interventional radiology



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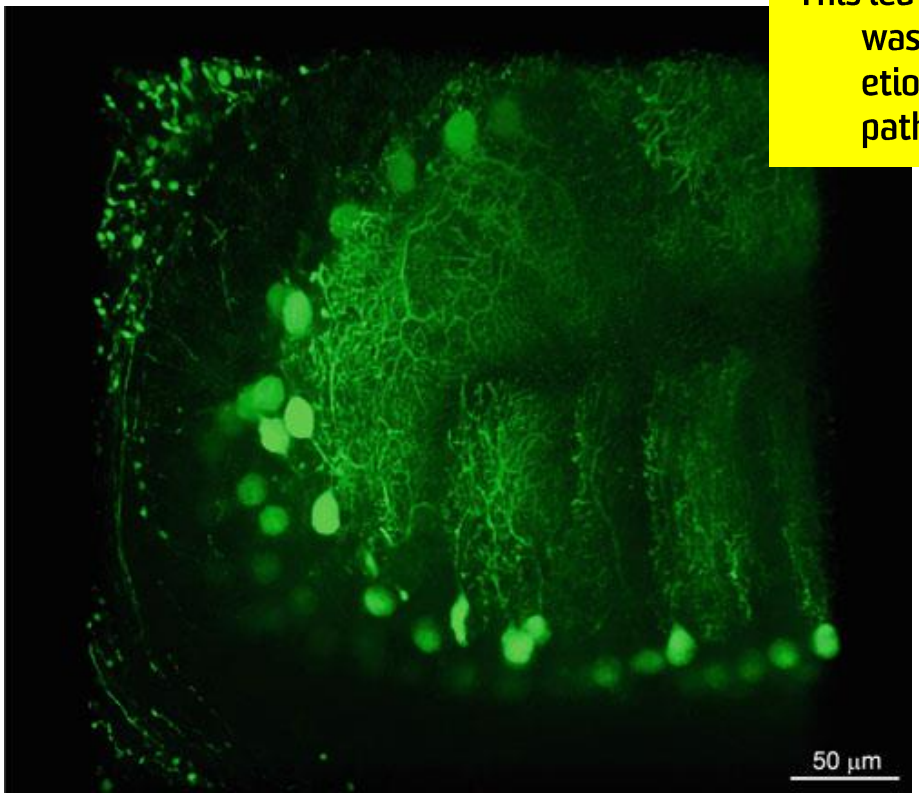
TARGET BACKGROUND

We discovered that alternative splicing of the **TRPC3 ion channels** in the brain produces a higher Ca^{2+} entry into neurons than was previously known (Kim et al. 2012 J Neuroscience).

This led us to realise that targeting the neuronalTRPC3 channels was likely to be neuroprotective in stroke and other brain injury etiologies where glutamate excitotoxicity contributes to pathology.



Craig, Housley, Fath (2014) - Multiphoton LSM imaging of Purkinje Neurons (GAD67-GFP mouse)

Glutamate released in excess with brain ischaemia (Stroke)

- **Activates mGluR (G protein-coupled glutamate receptor)**
- **Leads to activation of PLCB**
- **Leads to production of DAG and IP3**
- **DAG activates TRPC3 ion channels**
  - **sole effector of mGluR-mediated sustained depolarizing post-synaptic current in cerebellar Purkinje neurons (pn)**
  - **Block of sustained neuron depolarization and Ca2+ entry via the TRPC ion channels is a therapeutic target.**

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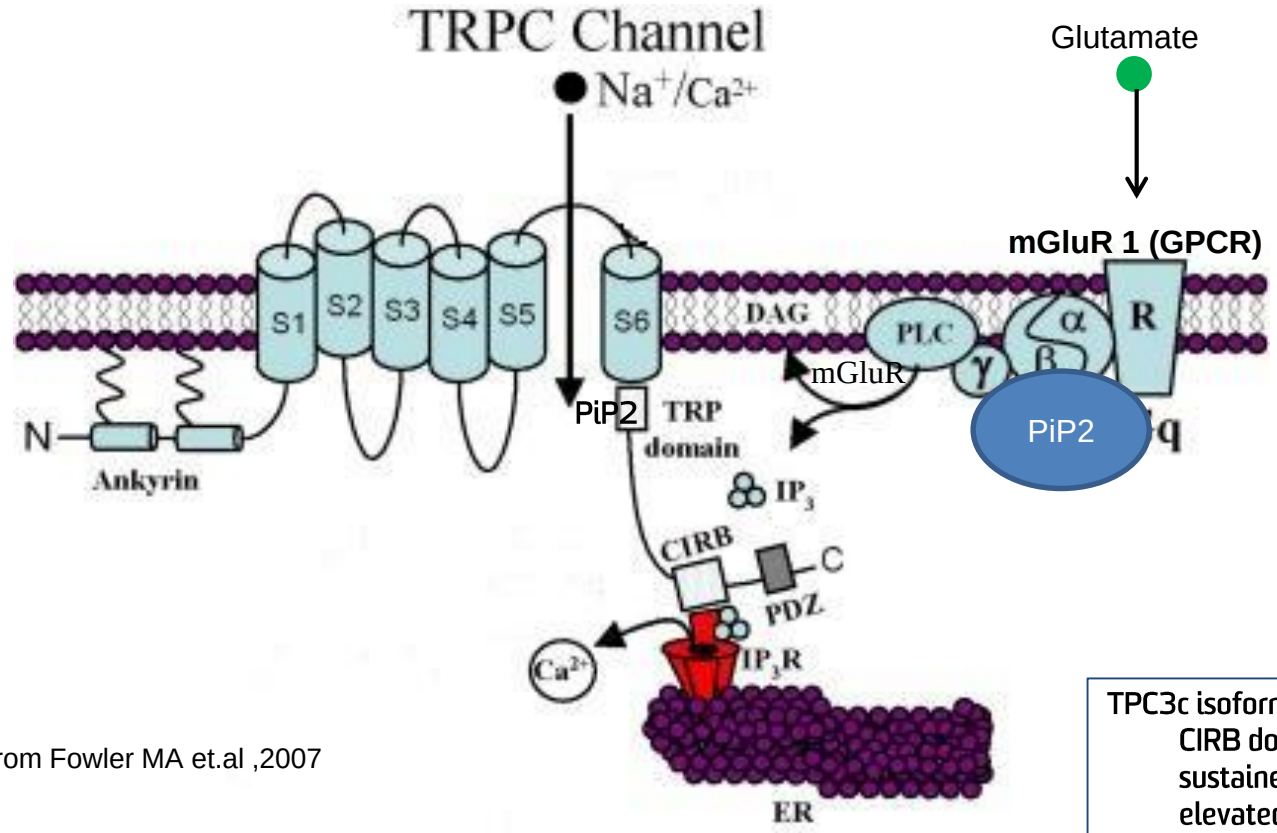
Transient Receptor Potential Canonical Channel (TRPC) - activation by mGluR



Adapted from Fowler MA et.al ,2007

TPC3c isoform lacks a functional CIRB domain – resulting in sustained Ca^{2+} entry with elevated cytosolic Ca^{2+}

Kim et al. J. Neurosci. 2012.

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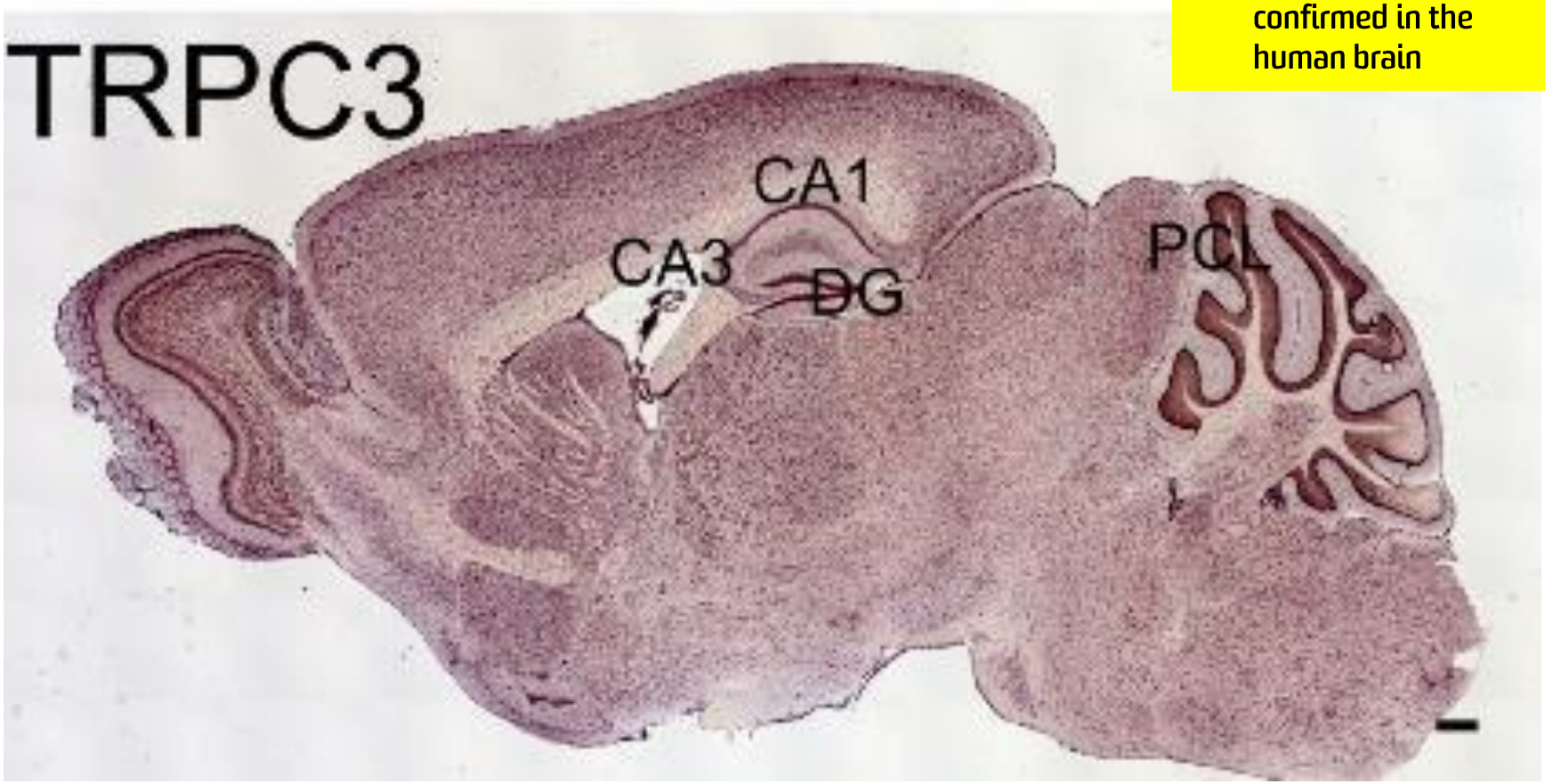
Localization of TRPC expression in cerebral cortex & cerebellum

***In situ* hybridisation**

TRPC3 variant expression confirmed in the human brain



Dong,2008

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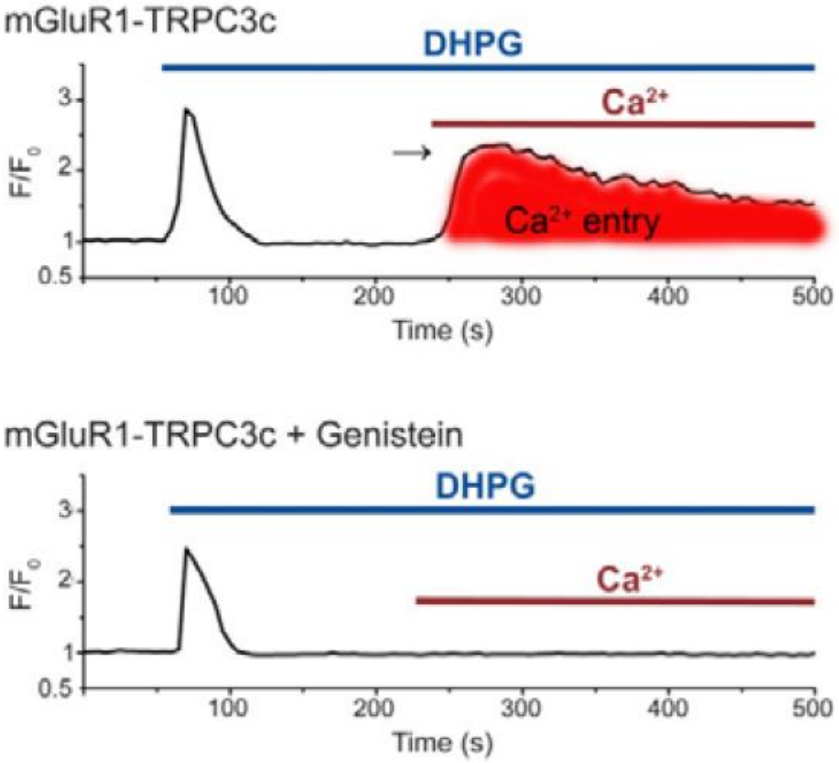
BACKGROUND – the isoflavone Genistein blocks Ca^{2+} entry mediated by the mGluR - TRPC3 ion channel pathway



Activation of TRPC3 channels by the mGluR1 agonist DHPG causes sustained Ca^{2+} entry. The figure shows Fluo 4 microfluorometry Ca^{2+} imaging data using HEK293 cells co-expressing mGluR1 and TRPC3c channels. DHPG is initially in Ca^{2+}-free media to deplete IP_3-mediated Ca^{2+} store release. When Ca^{2+} is returned to the chamber, Ca^{2+} entry through the activated TRPC channels is prominent (red highlight). The TRPC3-mediated Ca^{2+} entry is blocked by genistein (200 µM, lower trace). - after Kim et al. 2012.

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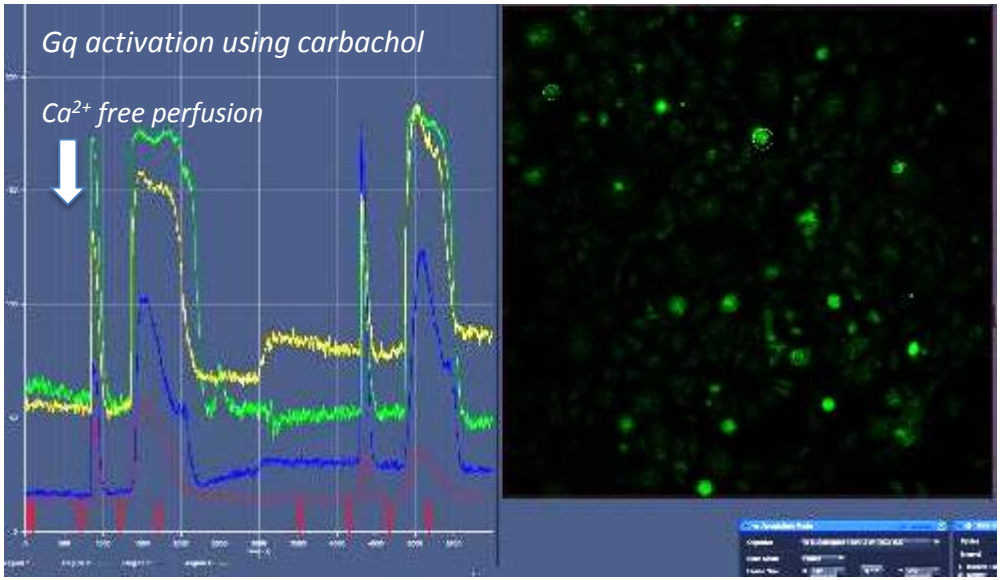
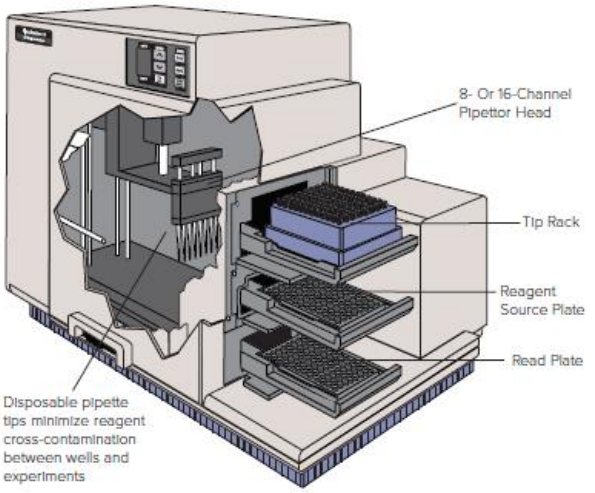
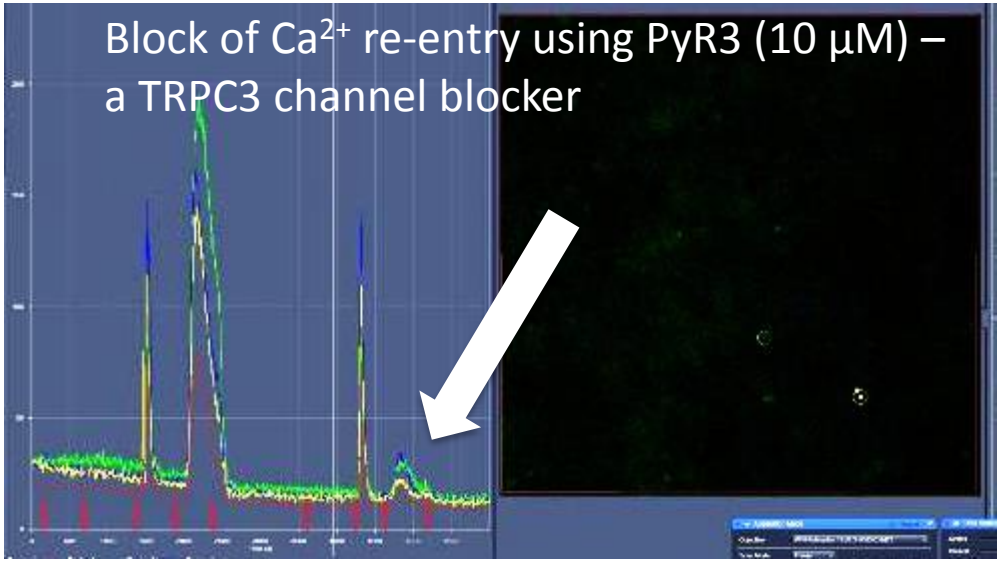
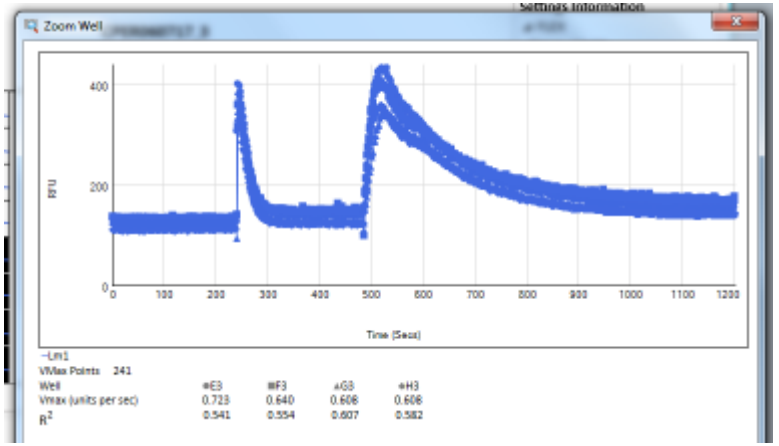
Drug Discovery program based on rHEK293-GCaMP5G Ca^{2+} reporter cell line





FlexStation 3 multi-modal microplate reader - Molecular Devices





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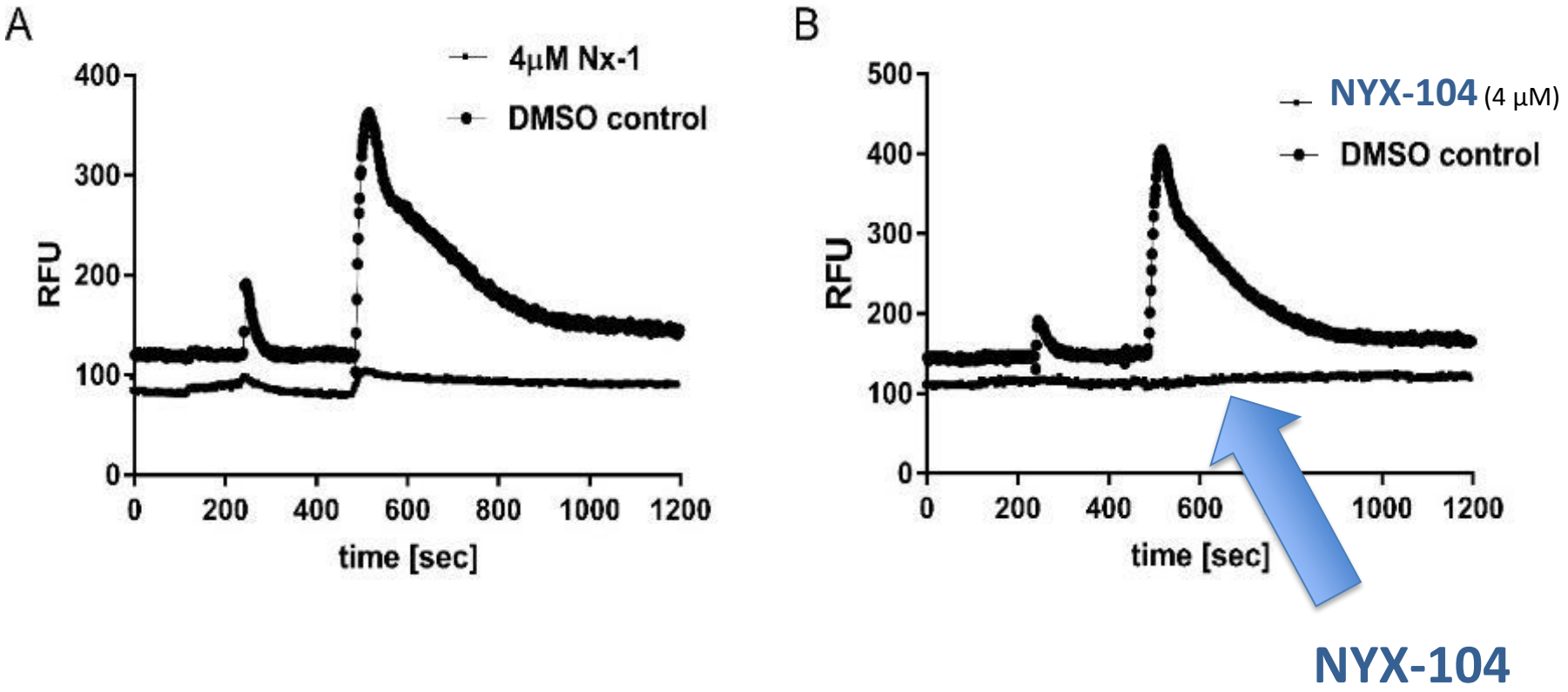
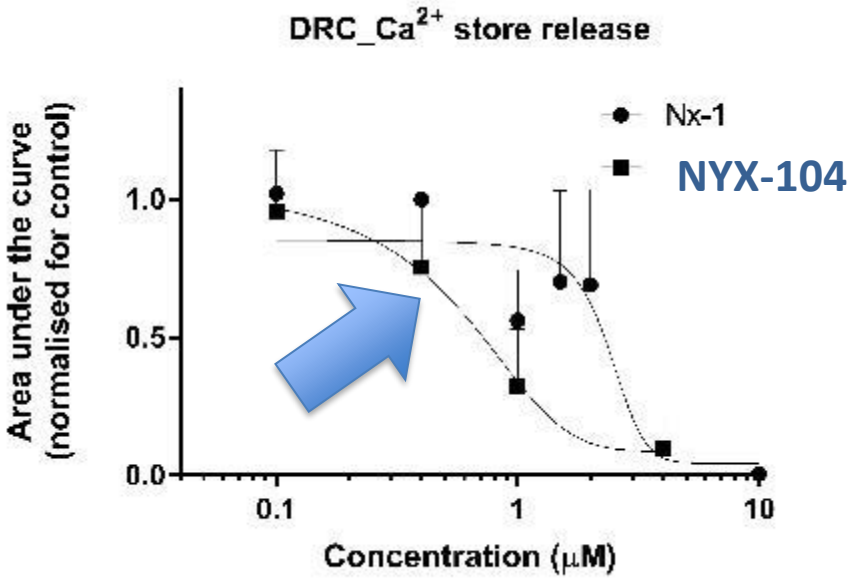
NYX-104 blocked Ca^{2+} dynamics of Gq signalling in HEK293 cells



Noxopharm unpubl. data

NYX-104 provided optimal block of Ca^{2+} dynamics of Gq signalling in HEK293 cells



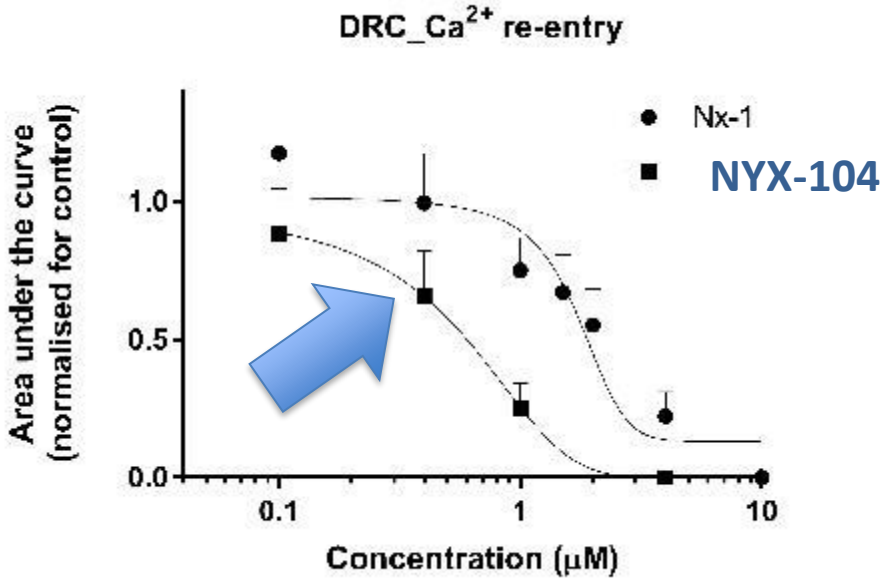


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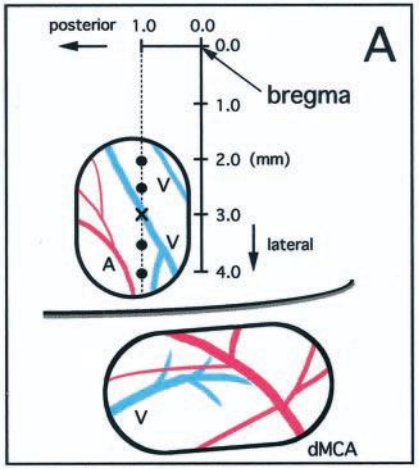
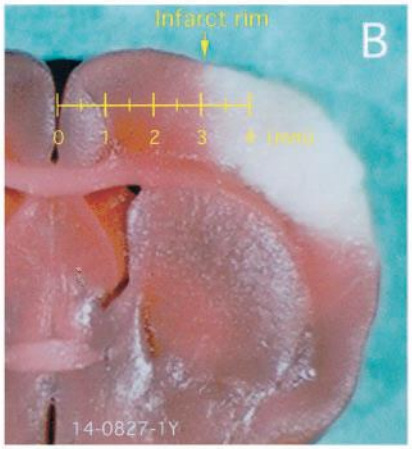
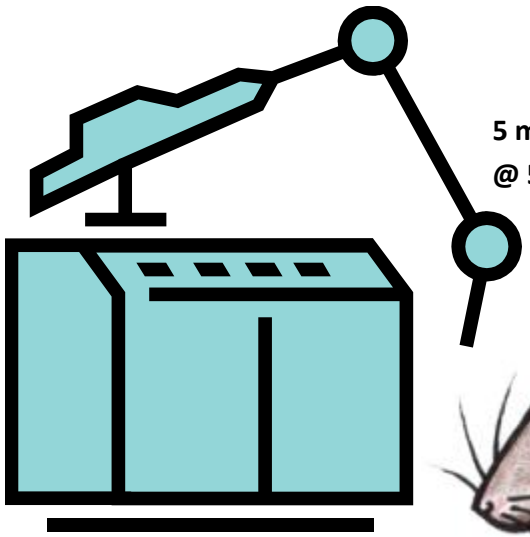
Photo-thrombotic stroke model







5 min illumination
@ 561 nm

Rose bengal

Yao et.al. 2003 Stroke

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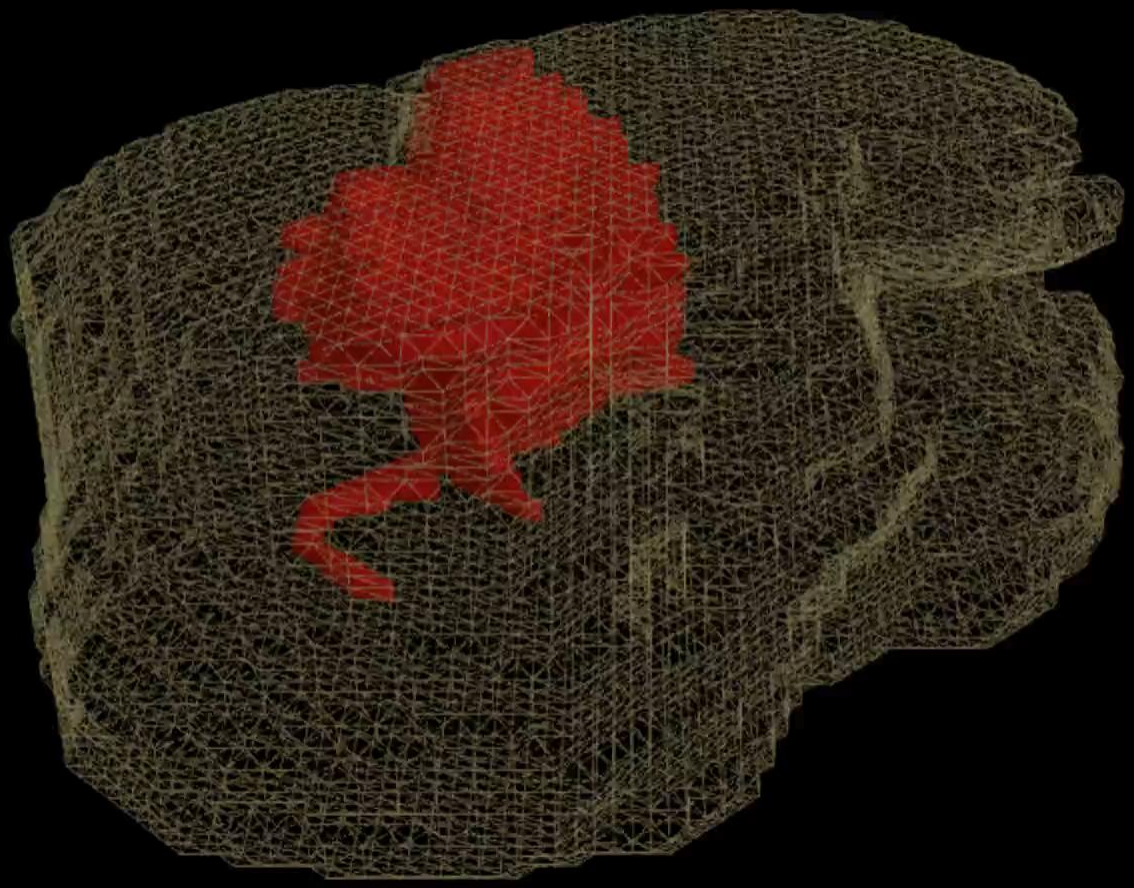
4DPI WT mouse
Photothrombotic lesion



Gorlamandala - Housley et al. unpubl

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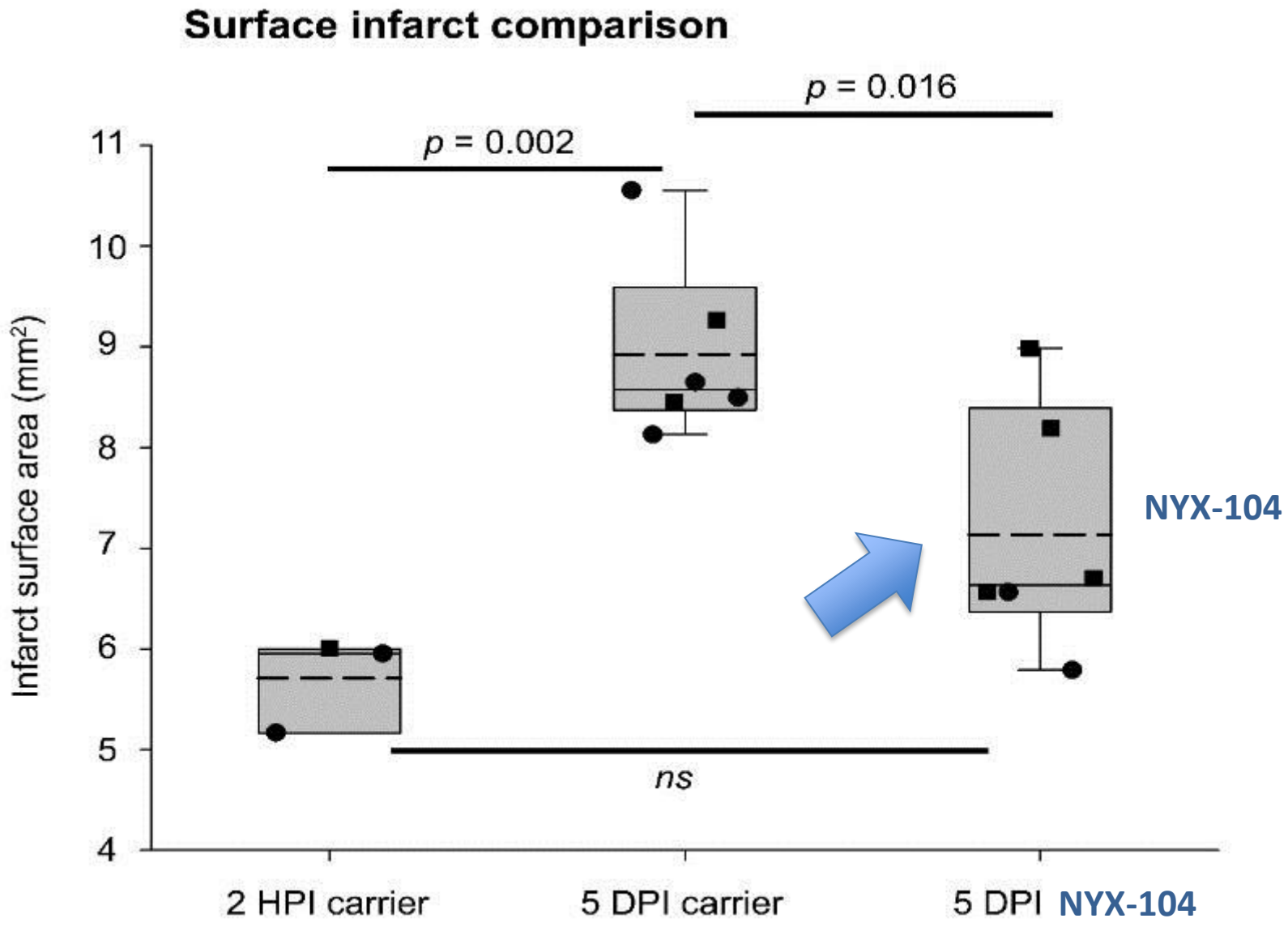

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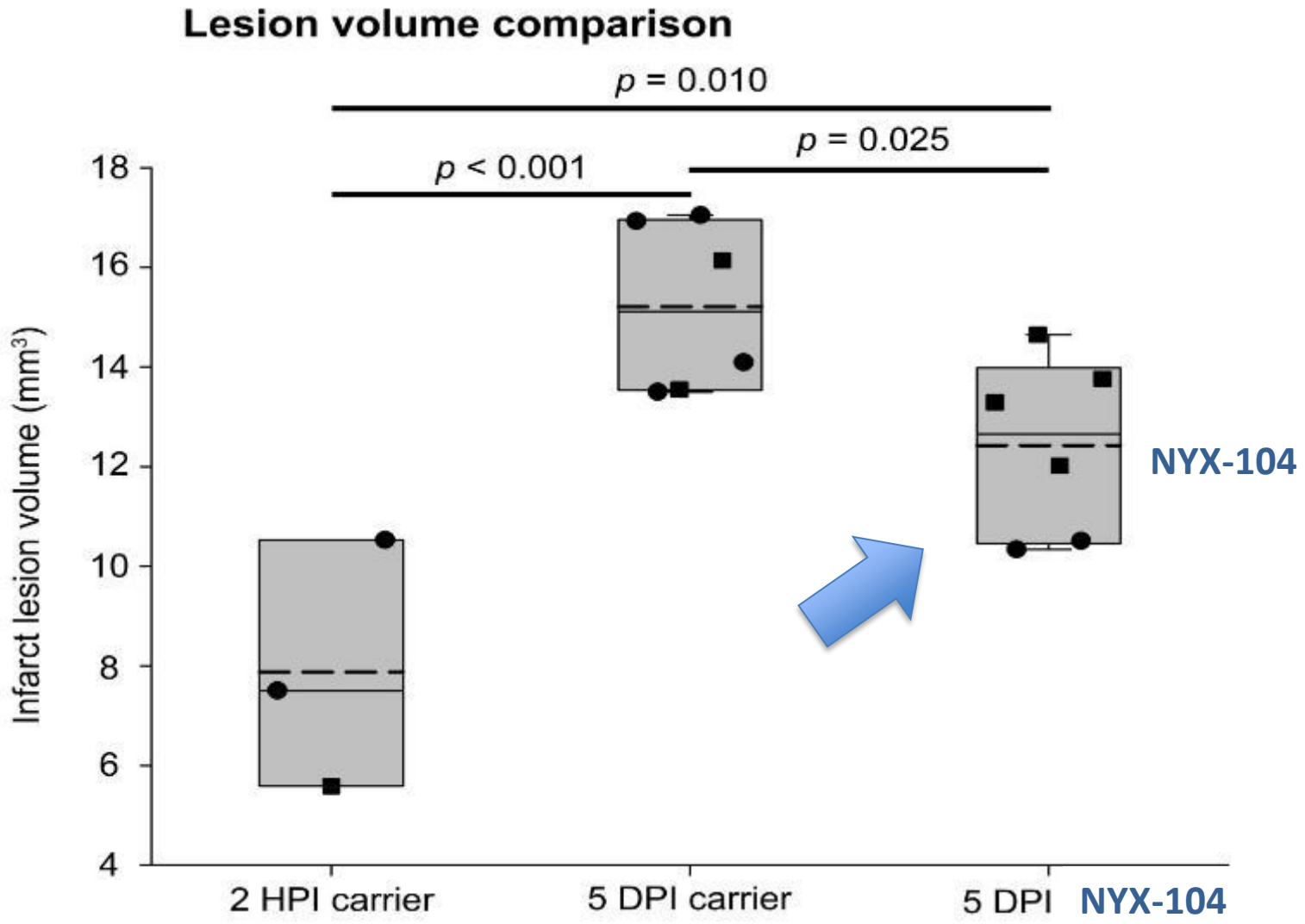

Noxopharm unpubl. data

CONCLUSIONS

- NYX-104 is very effective at blocking neuronal Ca^{2+} dynamics mediated by a dominant cell signalling pathway in neurons that is over-driven during brain injury associated with excessive release glutamate neurotransmitter. This arises in conditions such as stroke, epilepsy and brain trauma.

- NYX-104 can be delivered as a therapeutic treatment after brain injury via a Noxopharm – proprietary platform for systemic delivery, where it is effective in reducing the on-going glutamate excitotoxicity; the outcome in an experimental model of stroke is significantly reduced infarct size (neuroprotection).

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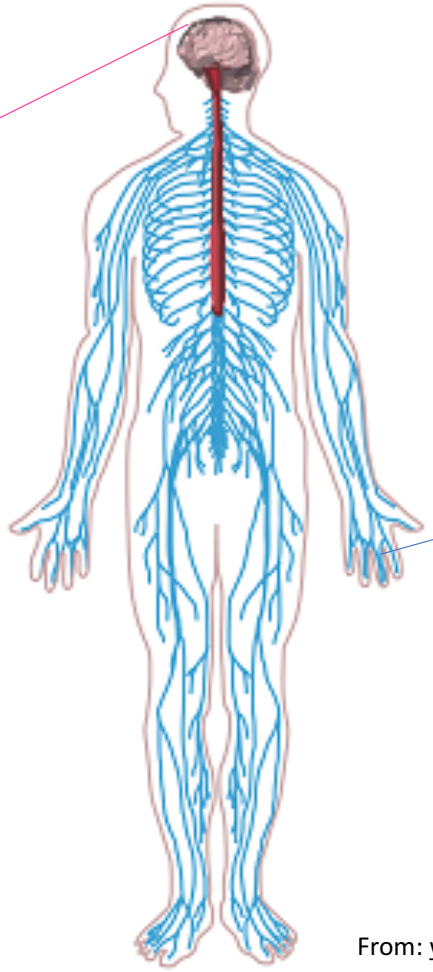
NYX-205 program and peripheral neuropathy

Dr Benny J. Evison

Noxopharm Non-Oncology Program Director

Central nervous system (CNS) = brain and spinal cord

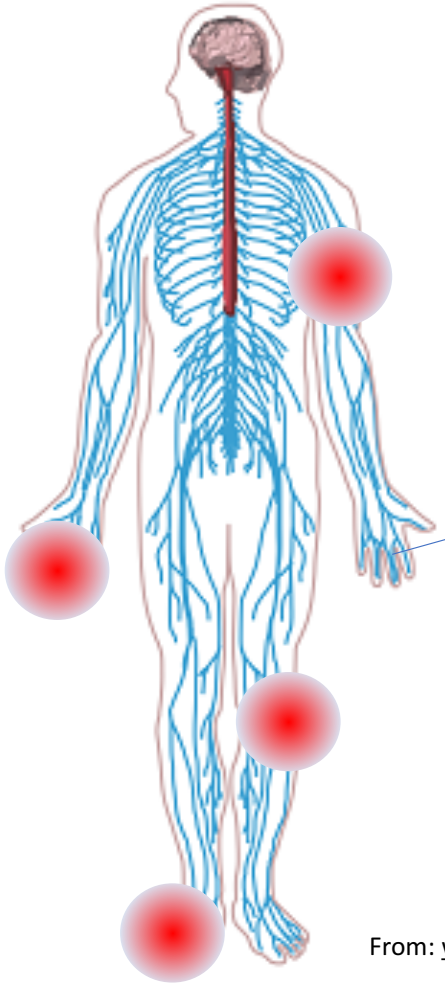


Peripheral nervous system = nerves outside CNS

From: www.study.com

Peripheral neuropathy

- Damage to these nerves = peripheral neuropathy
- Sensory symptoms:
  - tingling,
  - numbness,
  - burning sensations,
  - considerable pain



Peripheral nervous system = nerves outside CNS

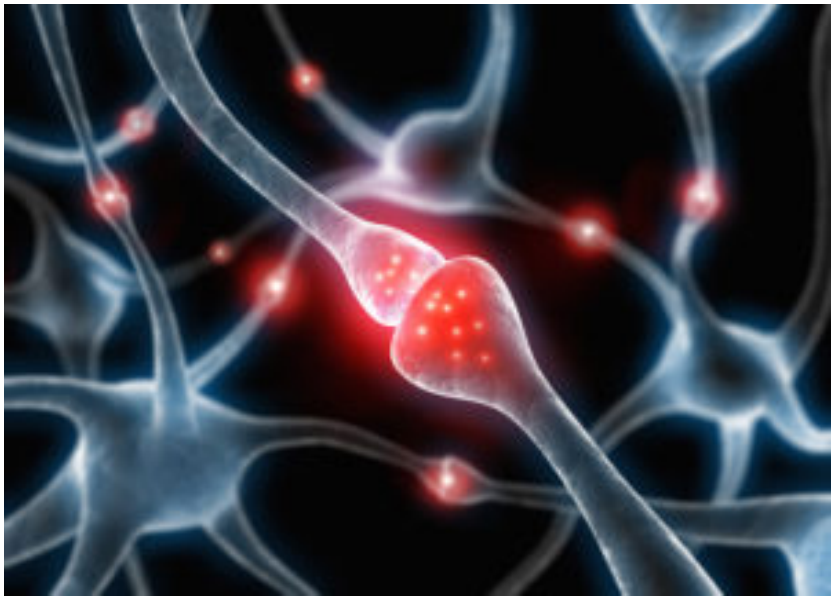
From: www.study.com

Peripheral neuropathy

- Associated with:
  - diabetes,
  - inflammatory bowel disease (IBD),
  - traumatic injury,
  - treatment with certain cancer medications

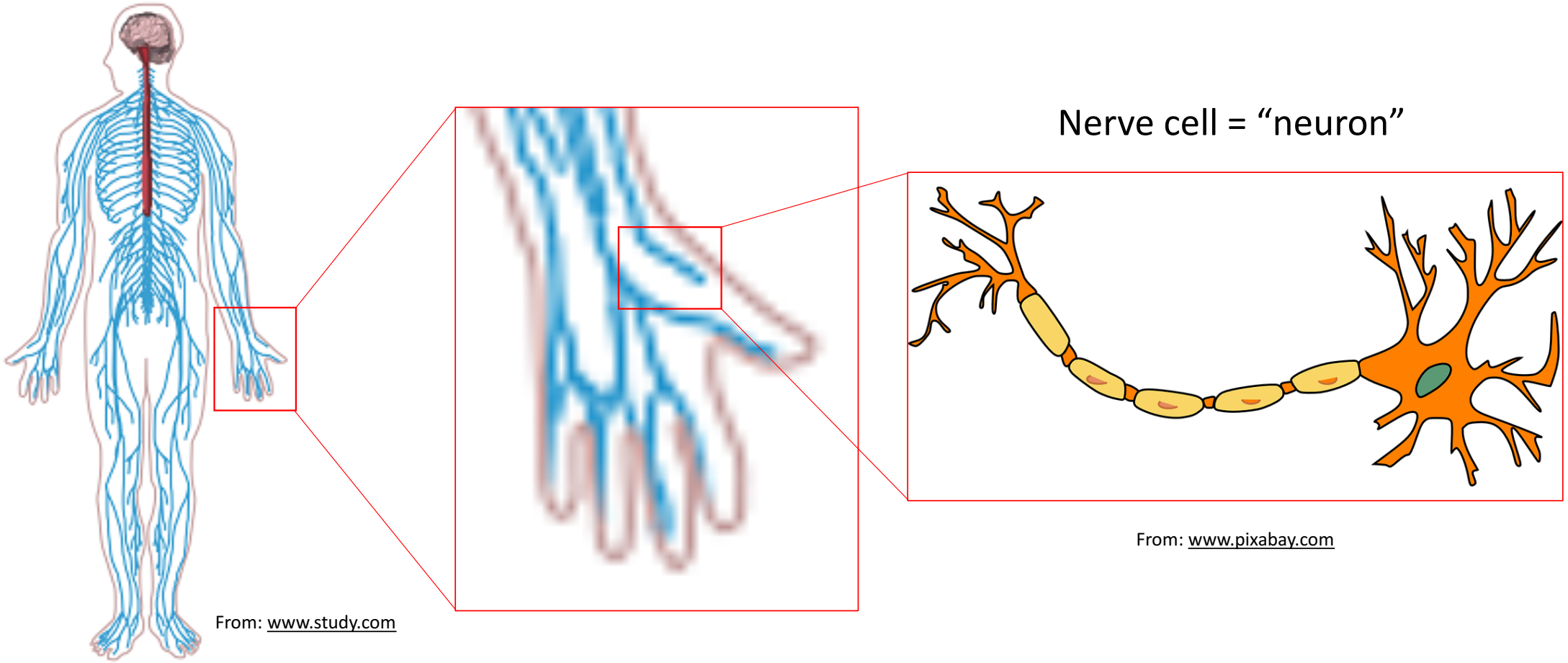
Chemotherapy induced peripheral neuropathy (CIPN)

- Acute or chronic
- Affects 30 – 70% of people receiving chemotherapy
- Can result in chemotherapy cessation
- No effective prophylactic or therapeutic treatment
- Nyrada Inc's initial goal is to deliver an effective treatment



From: www.veteranslawblog.org

Chemotherapy induced peripheral neuropathy (CIPN)



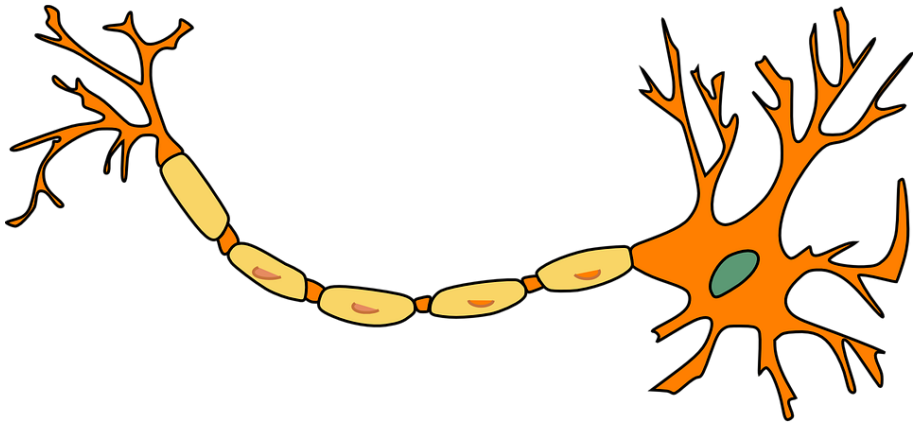
From: www.study.com

Nerve cell = “neuron”

From: www.pixabay.com

Chemotherapy induced peripheral neuropathy (CIPN)

- Neurons are susceptible to cancer chemotherapies, e.g. paclitaxel



From: www.pixabay.com

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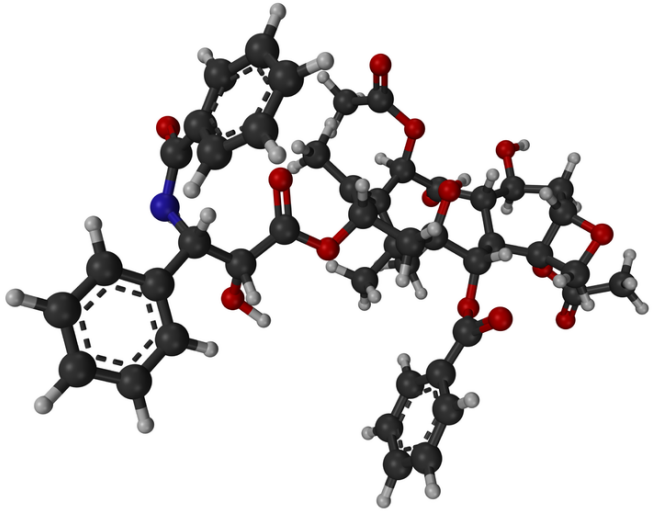

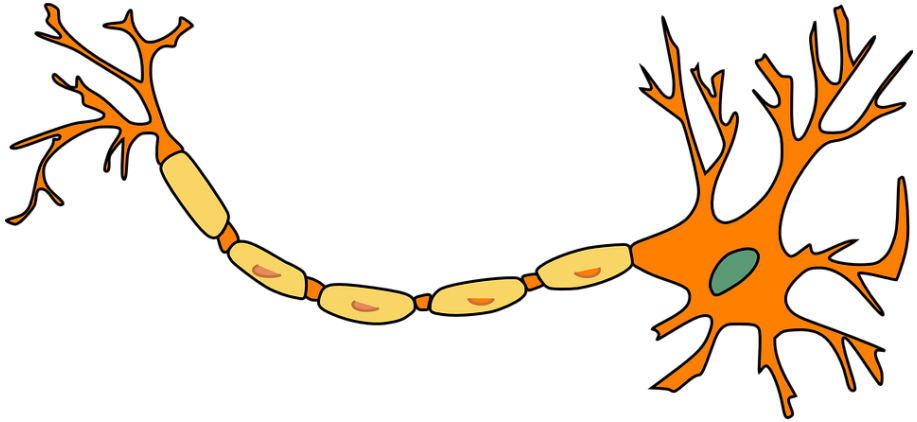

From: www.pixabay.com

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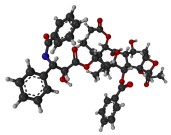
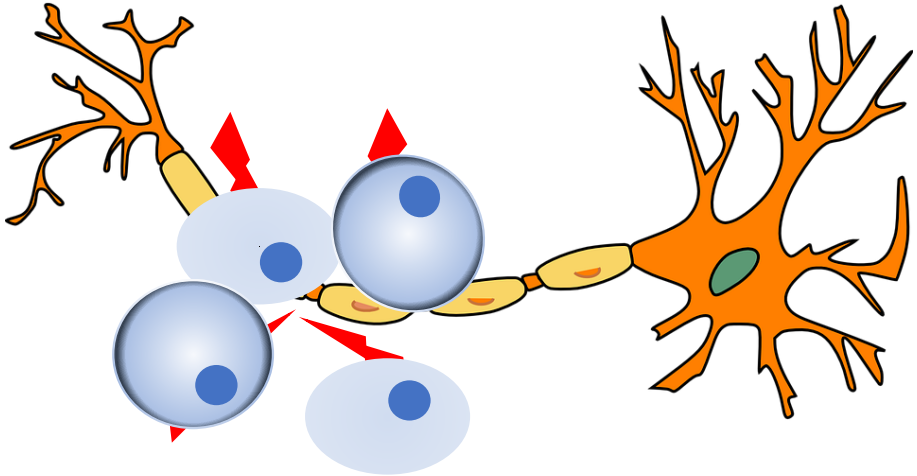
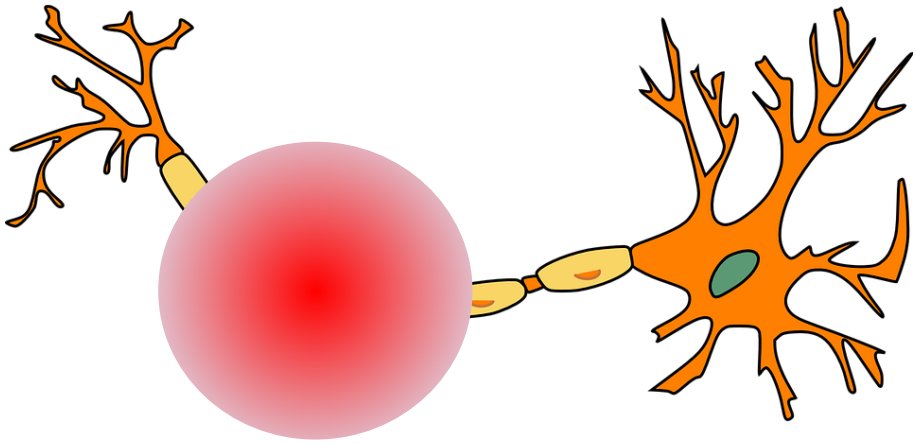




From: www.pixabay.com

Chemotherapy induced peripheral neuropathy (CIPN)

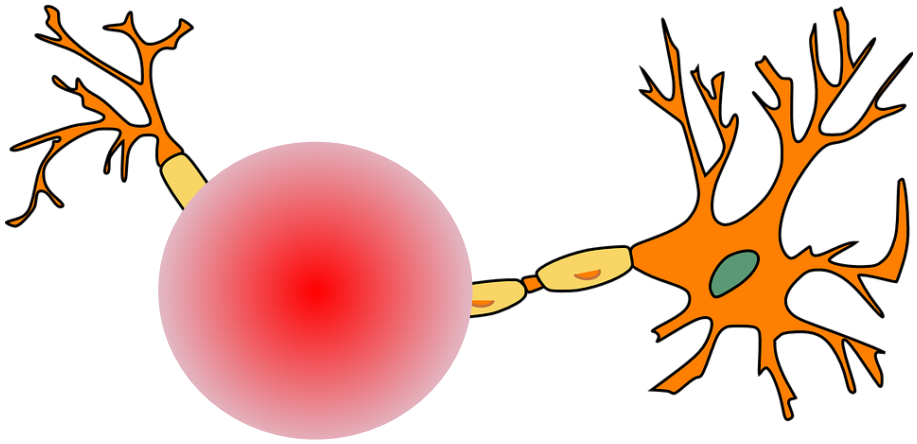
- Neuroinflammation



From: www.pixabay.com

NYX-205 as a treatment for CIPN

- NYX-205 has shown promise as a therapy for inflammatory diseases
- But not neuroinflammatory diseases

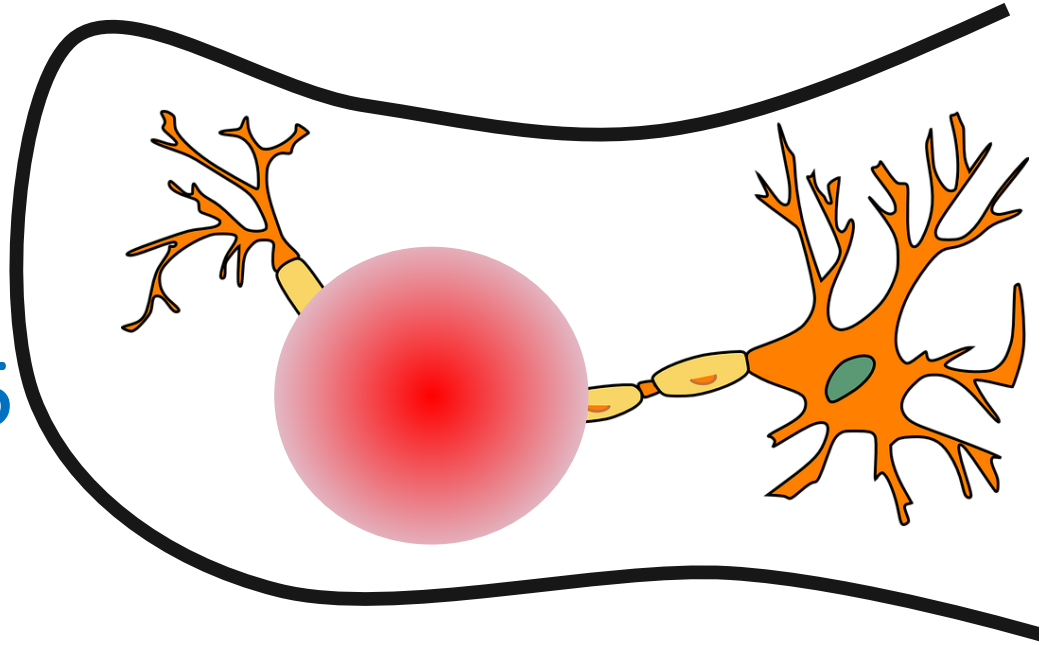


From: www.pixabay.com

NYX-205 as a treatment for CIPN

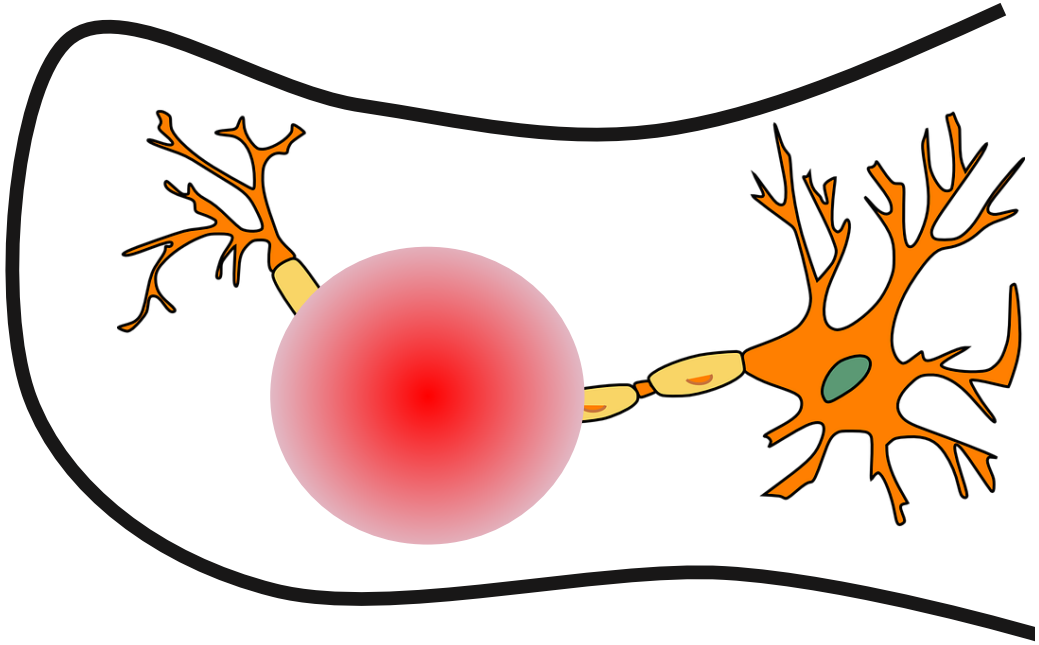
- Why?
- Blood-nerve barrier

NYX-205 NYX-205



NYX-205 as a treatment for CIPN

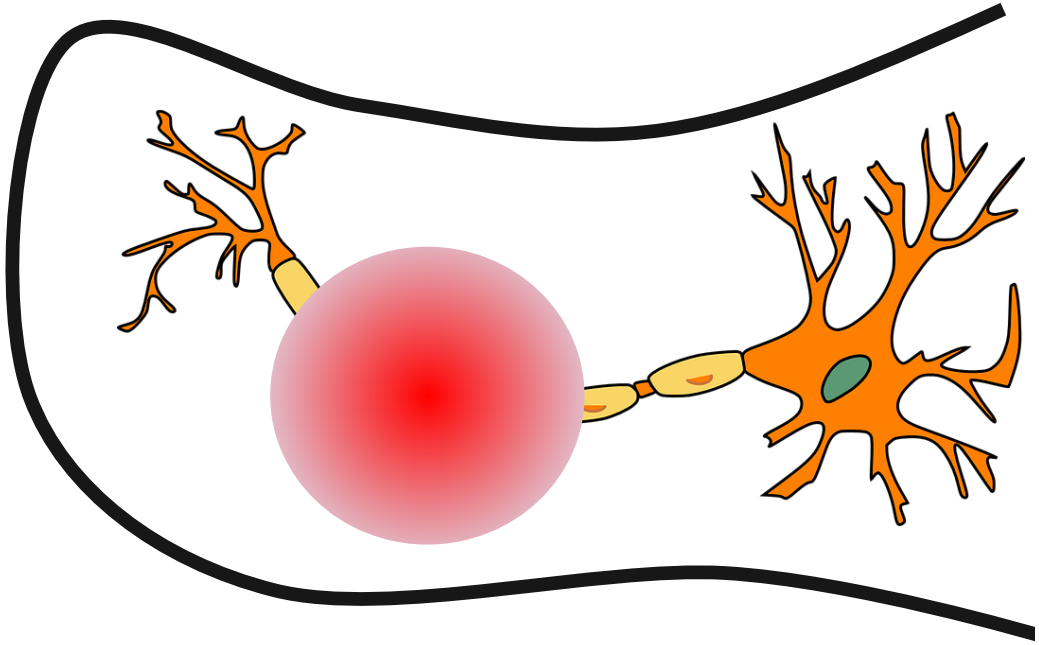
- LIPROSE technology as a solution
- Lipid protective shield
  - Used by Noxopharm to deliver idronoxil into the brain



NYX-205 as a treatment for CIPN

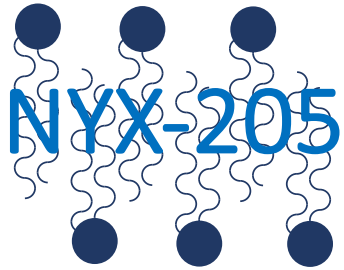
- LIPROSE technology as a solution

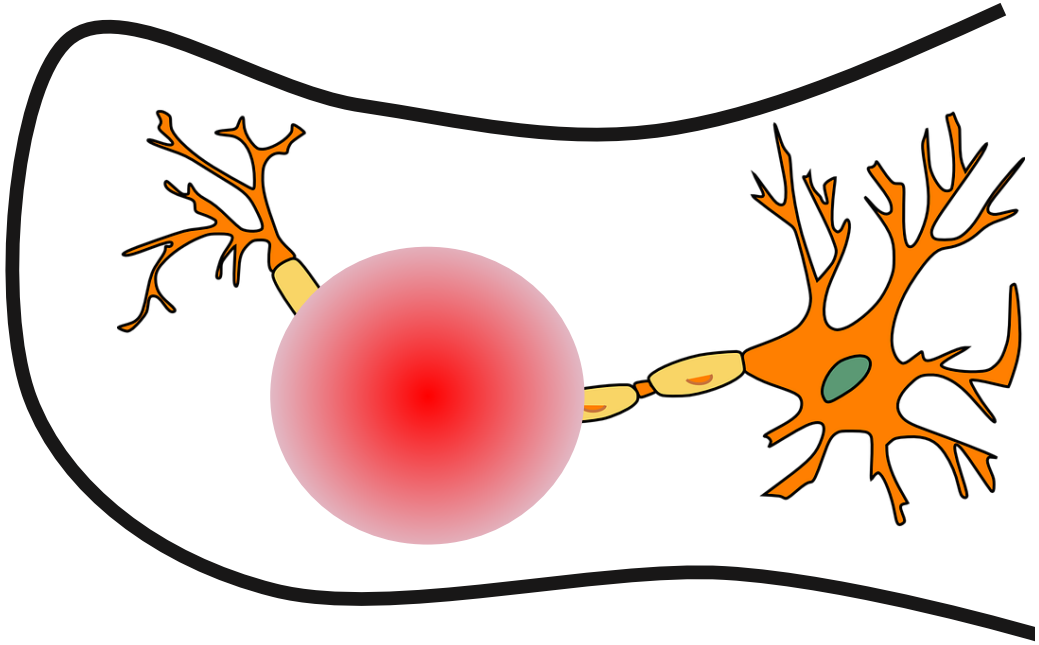
NYX-205



NYX-205 as a treatment for CIPN

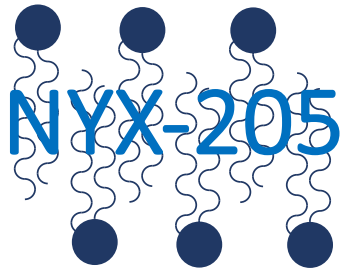
- LIPROSE technology as a solution
- Lipid = 

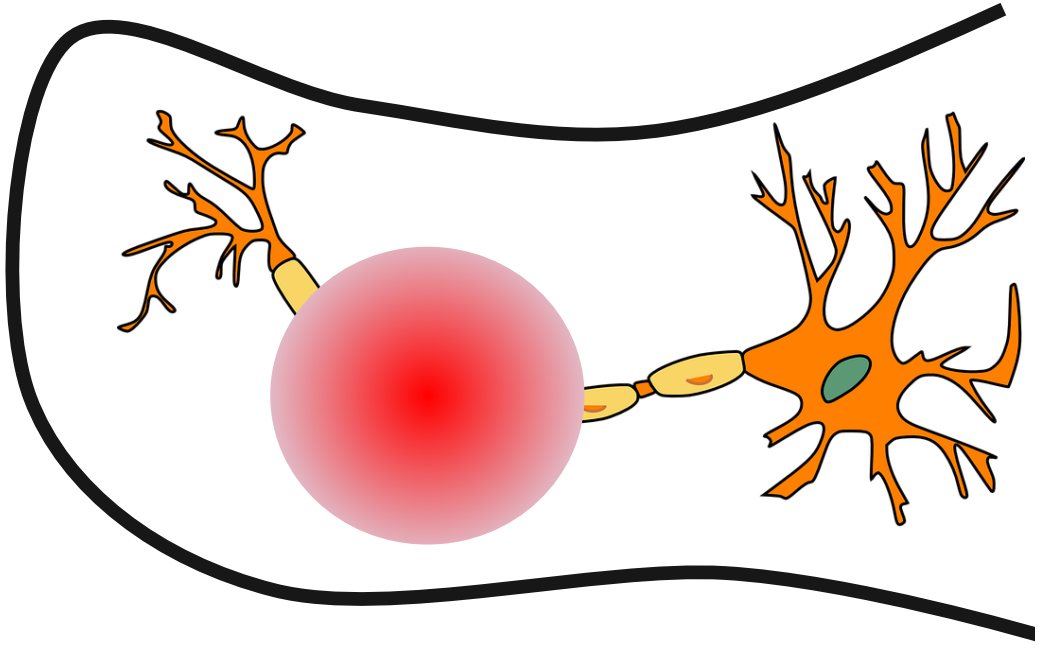




NYX-205 as a treatment for CIPN

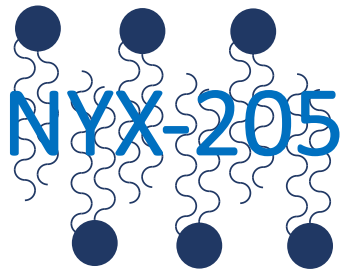
- Lipid-NYX-205 traverses blood nerve barrier

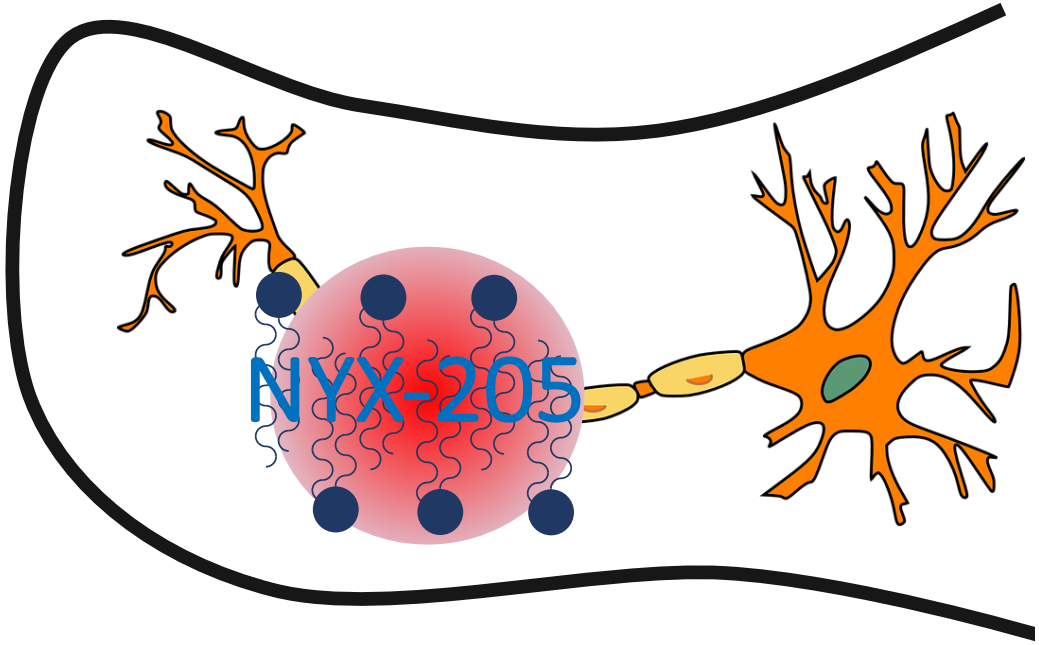




NYX-205 as a treatment for CIPN

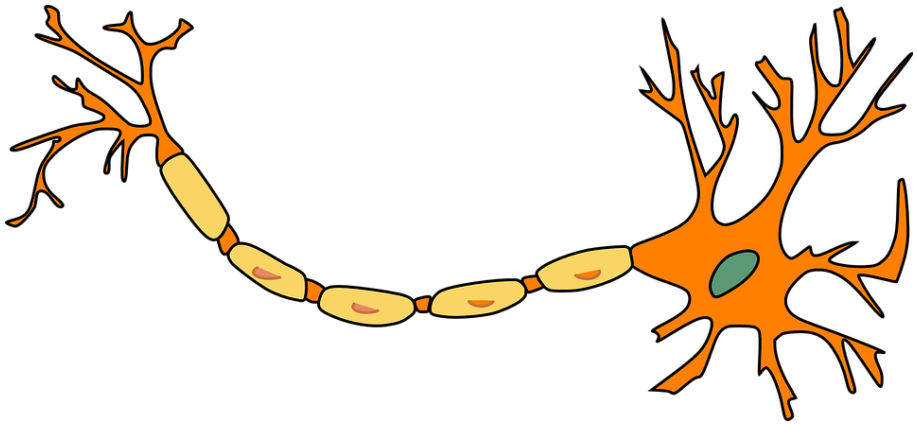
- Neuroinflammation subsides





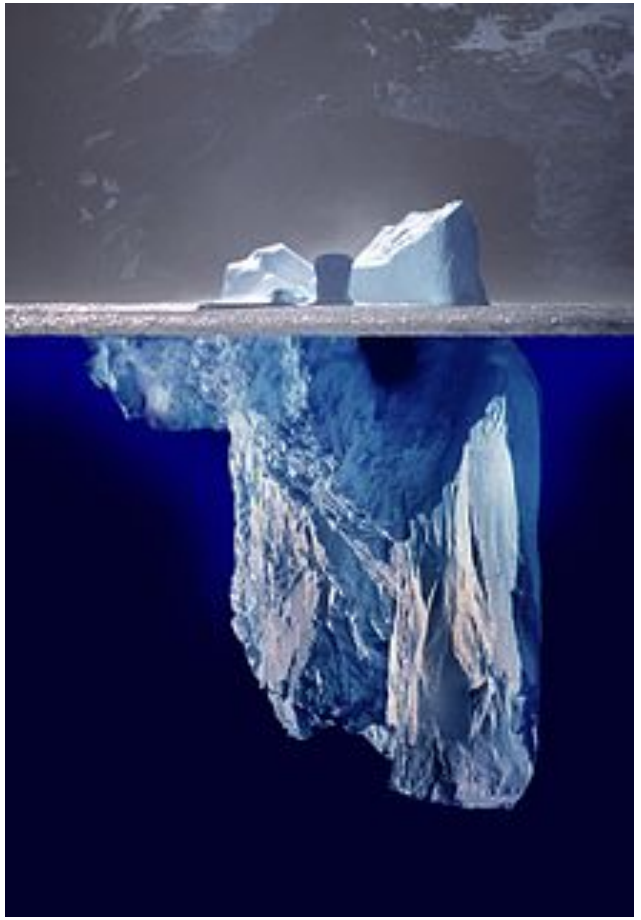
Summary

- CIPN associated with neuroinflammation,
- No therapy exists,
- NYX-205 has established anti-inflammatory properties,
- LIPROSE will be applied to help NYX-205 traverse blood nerve barrier:
  - To enable a therapeutic effect



An eye on the future

- Other diseases are neuroinflammatory,
  - Alzheimer's disease,
  - motor neuron disease,
  - multiple sclerosis, etc.
- Nyrada Inc is evaluating these indications as targets of NYX-205/LIPROSE



From: www.wiktionary,org

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Cardio Therapeutics Pty Ltd and the PCSK9 inhibitor drug program

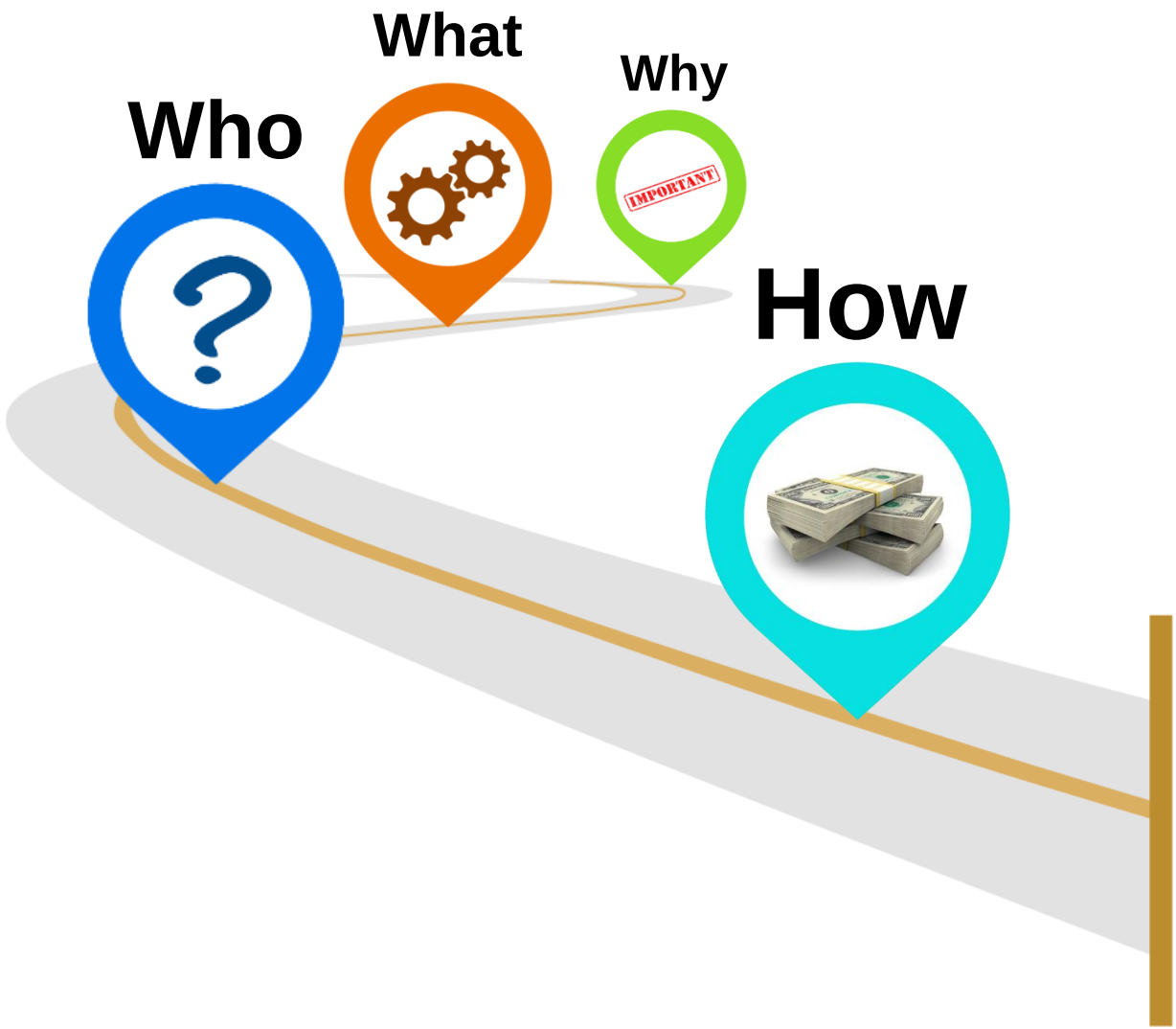
Cardio Therapeutics is part of the Altnia Group and subject to acquisition by Nyrada Inc.

Version v1.1

Forward Looking Statements

This document may contain forward-looking statements. You can identify these statements by the fact they use words such as “aim”, “anticipate”, “assume”, “believe”, “continue”, “could”, “estimate”, “expect”, “intend”, “may”, “plan”, “predict”, “project”, “plan”, “should”, “target”, “will” or “would” or the negative of such terms or other similar expressions. Forward-looking statements are based on estimates, projections and assumptions made by Altnia about circumstances and events that have not yet taken place. Although Altnia believes the forward-looking statements to be reasonable, they are not certain. Forward-looking statements involve known and unknown risks, uncertainties and other factors that are in some cases beyond the Company’s control that could cause the actual results, performance or achievements to differ materially from those expressed or implied by the forward-looking statement. No representation, warranty or assurance (express or implied) is given or made by Altnia that the forward-looking statements contained in this announcement are accurate and undue reliance should not be placed upon such statements.

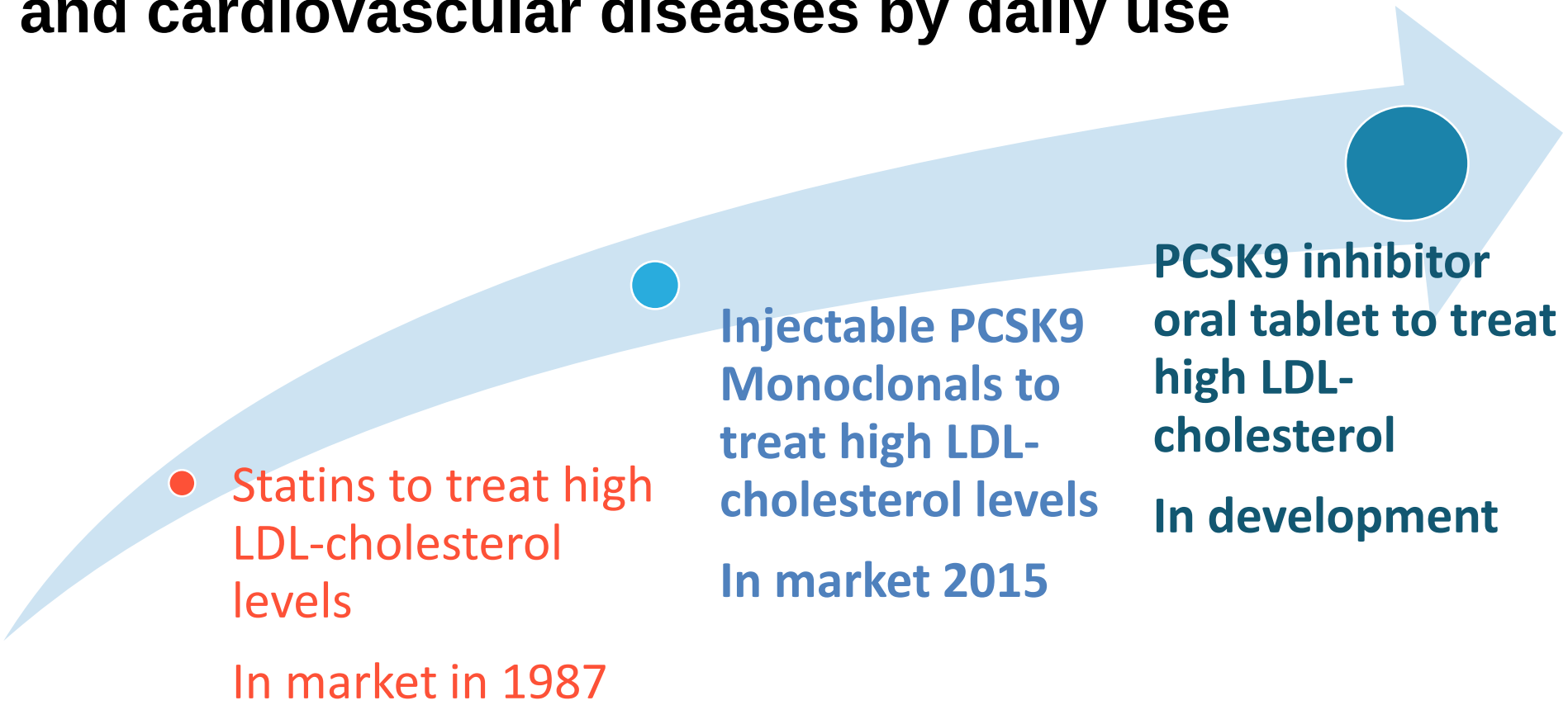
The PCSK9 story outline



An important & valuable new treatment for atherosclerosis and cardiovascular disease

Our goal is to :

Have a tablet (oral) drug to target and inhibit PCSK9-LDL Receptor interaction to treat hypercholesterolemia (high LDL-cholesterol levels) and cardiovascular diseases by daily use



Why is this important

- The medical need is large

Hypercholesterolemia - also called high cholesterol :-

- cholesterol (a sterol) is essential for our body
- cholesterol is carried in our blood in lipoproteins (fat protein)
- lipoproteins are named after their density - very low density lipoprotein (VLDL), low density lipoprotein (LDL), intermediate density lipoprotein (IDL) and high density lipoprotein (HDL)
- HDL is “good” lipoprotein – the rest are “bad”
- high levels of LDL-cholesterol are linked to an increased risk of atherosclerosis and coronary heart disease
- the National Institutes of Health says that 34 million Americans have elevated “bad” blood cholesterol levels *

* https://ghr.nlm.nih.gov/condition/hypercholesterolemia#statistics

Why is this important

- The medical need is large

Atherosclerosis (arteriosclerotic vascular disease) * :-

- atherosclerosis is a disease in which plaque builds up inside your arteries
- arteries are blood vessels that carry oxygen-rich blood to your heart and other parts of your body
- cells in your body (brain, muscles etc.) rely upon oxygen to function
- atherosclerosis limits the flow of oxygen-rich blood to cells that make your body work well
- atherosclerosis starts off as debilitating and restricting activity
- more severe blockage can lead to serious problems, including heart attack (ischemic heart disease (IHD)), ischemic stroke, and death
- ischemic heart disease remains the leading cause of premature adult mortality worldwide **

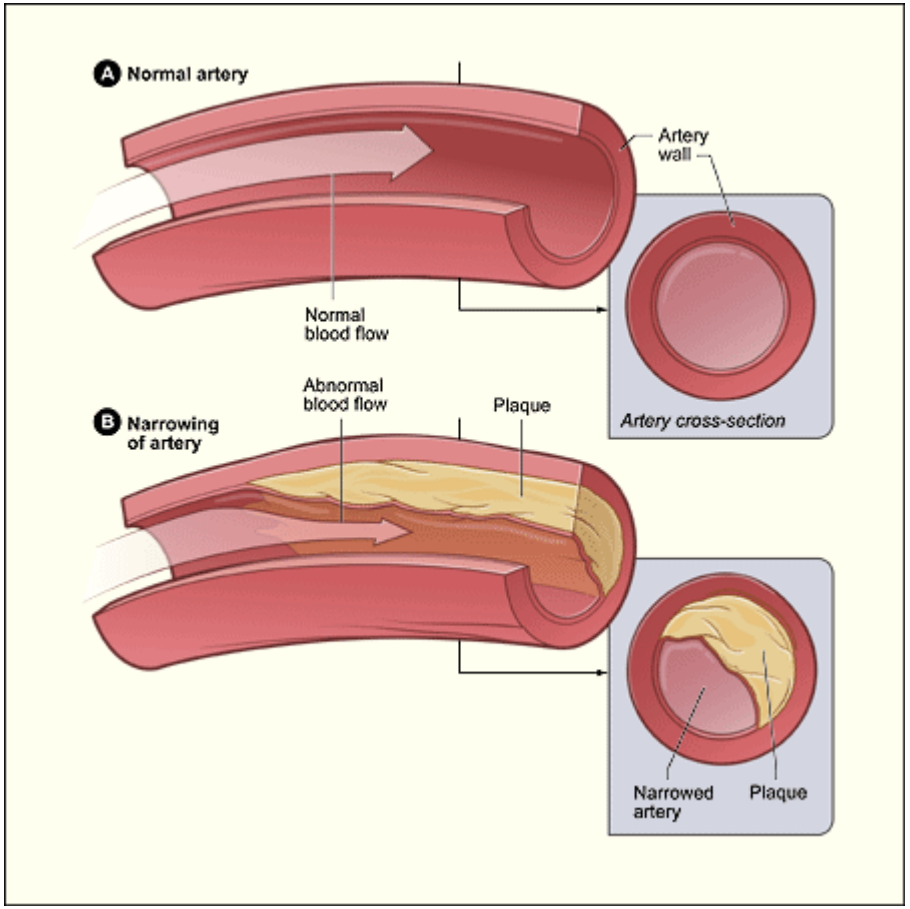
* https://www.nhlbi.nih.gov/health/health-topics/topics/atherosclerosis

** Lancet. 2015 Jan 10;385(9963):117-71. doi: 10.1016/S0140-6736(14)61682-2. Epub 2014 Dec 18. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013

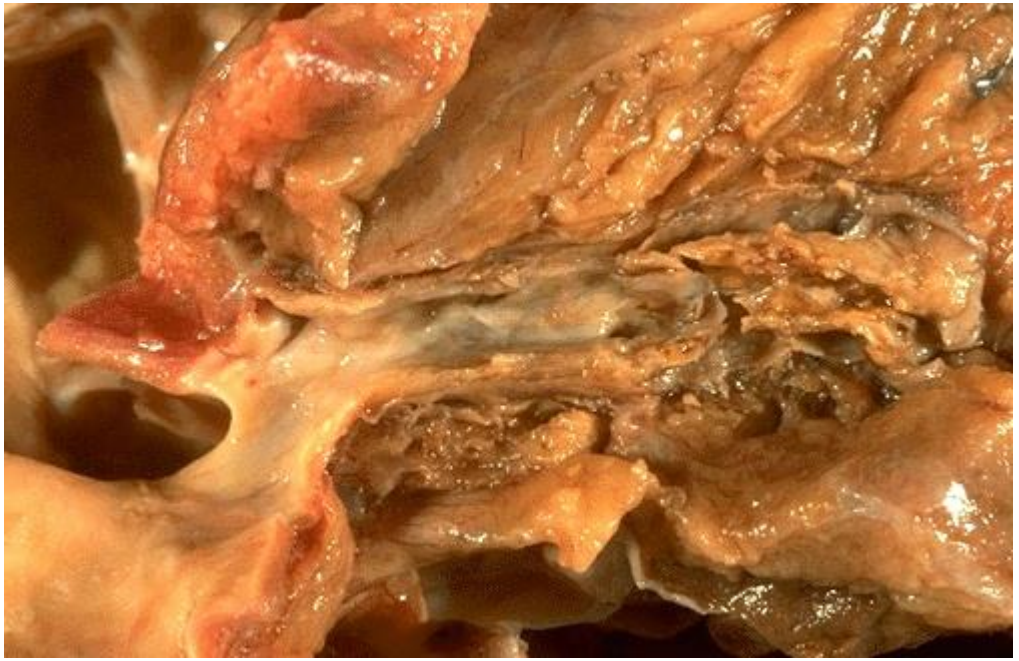
Why is this important

- The medical need is large

Atherosclerosis (arteriosclerotic vascular disease)



www.nhlbi.nih.gov/health/health-topics/topics/atherosclerosis



https://library.med.utah.edu/WebPath/ATHHTML/ATH006.html

Why is this important

- The medical need is large

Coronary heart disease – the most common cause of heart attacks

- stable plaques cause angina and pain, anxiety and discomfort – and in more severe cases a loss of mobility and independence
- unstable plaques can lead to a blood clot and heart attack or stroke
- causes about one-third of all deaths in people older than 35 years *
- the 2016 Heart Disease and Stroke Statistics from the American Heart Association (AHA) has recently reported that 15.5 million persons ≥20 years of age in the USA have CHD **
- CHD affects around 1.2 million Australians, is the single leading cause of death in Australia, claimed the lives of 19,777 Australians (12% of all deaths) in 2015 and kills one Australian every 27 minutes ***

* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4958723

** Circulation. 2016 Jan 26;133(4):447-54. doi: 10.1161/CIR.0000000000000366 Executive Summary: Heart Disease and Stroke Statistics--2016 Update: A Report From the American Heart Association.

*** https://www.heartfoundation.org.au/about-us/what-we-do/heart-disease-in-australia

Why is this important

- The medical need is large

  Cardiovascular disease *

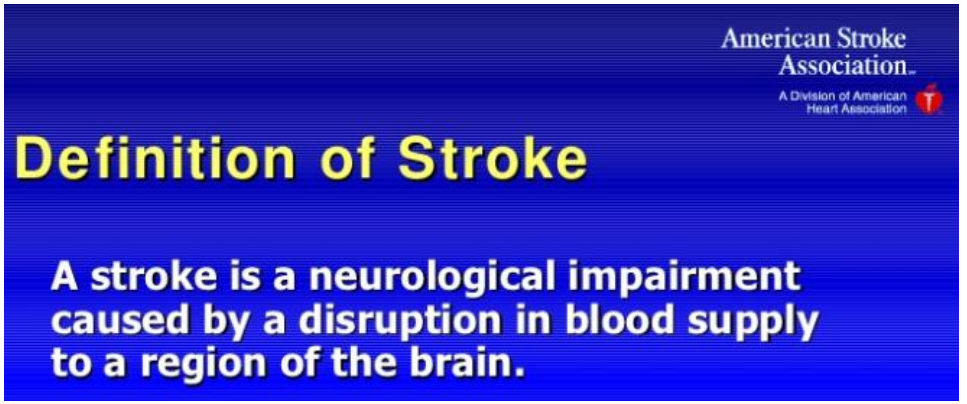
  - kills one Australian every 12 minutes.
  - affects one in six Australians or 4.2 million people
  - was the main cause for 490,000 hospitalisations in 2014/15.
  - claimed the lives of 45,392 Australians (nearly 30% of all deaths) in 2015 - deaths that are largely preventable

* www.heartfoundation.org.au/about-us/what-we-do/heart-disease-in-Australia

Why is this important

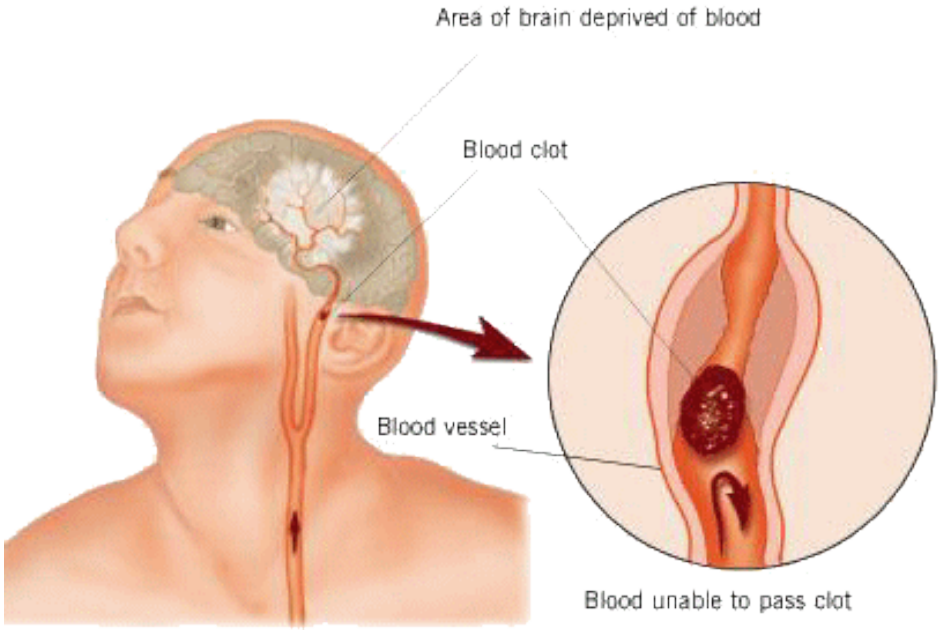
- The medical need is large

Ischemic stroke occurs when the blood supply to part of the brain is suddenly blocked



"In the U.S. it is estimated that 6.4 million adults have suffered a stroke and another 13 million may have experienced a "silent stroke," loss of brain cells without visible symptoms.

In the U.S., the financial burdens associated with stroke treatment and recovery is estimated at $73 billion dollars in 2010"



http://brainjury.org/blog/brain-injuries/stroke

Why is this important

- The present treatments to reduce LDL-cholesterol
  - Diet, smoking & lifestyle (exercise)
    - Some people have a genetic predisposition that diet etc. cannot resolve, others are unable to achieve control
  - Statins – Atorvastatin (Lipitor™), Fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin
  - Biologic PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitor drugs approved by FDA (USA) and EMA (Europe)*
    - evolocumab (Repatha™) (Amgen),
    - alirocumab (Praluent™) (Sanofi/Regeneron)

* Approved for use in patients with heterozygous and homozygous familial hypercholesterolemia and for patients intolerant of statins or those with a major risk of cardiovascular disease (CVD) but unable to lower their LDL cholesterol (LDL-C) to optimal levels with statins and ezetimibe www.ncbi.nlm.nih.gov/pubmed/27186592

Why is this important

It is a huge commercial opportunity

- Statins
  - were originally discovered from fungi
  - are now off patent (generics) and cheap
  - reached a peak of US$19 billion sales p.a. (2005)
  - have safety and toxicity problems * “a sizable proportion of statin-treated patients does not achieve recommended target LDL cholesterol levels, and some discontinue treatment owing to drug-related side effects”
  - work as HMG-CoA reductase inhibitors **
- Biologic PCSK9 drugs are :-
  - new (approved in 2015 & 2016) but expensive (~ US$14,000 p.a.) ***
  - require injection every 2 weeks
  - have demonstrated excellent safety and efficacy data since approvals in USA and EU
  - work by inhibiting PCSK9 binding to LDL Receptor

No known small molecule drug inhibiting PCSK9 is in clinical trials

So there is room for our PCSK9 program – tablet form of PCSK9 inhibitor

* Monoclonal antibodies are shown to be safe and effective in patients with dyslipidaemia BMJ 2015; 350 doi: https://doi.org/10.1136/bmj.h2251l ** see https://en.wikipedia.org/wiki/Statin *** www.medscape.com/viewarticle/884624

What we are doing

How new drugs are brought forward

- The old approach
  - many old drugs came from medicines derived from natural sources (hit-n-miss medicine over many years) e.g. penicillin from mould (antibiotic) and quinine from bark of the cinchona tree (anti malaria)
  - then there is High Throughput Screening (HTS) - laboratory-based screening libraries (thousands to millions) of compounds tested against disease-specific tests ("assays") against a "target" and looking for "hits" that could become a drug to treat a disease (also hit-n-miss)
- The newer approach
  - based upon the dramatic reduction in cost & time in genomic sequencing (US$2.7 billion and 15 years (starting 1990) vs. ~ US$1,000 and weeks (now)
  - looking at the differences between patient-groups and their genomics
  - the idea is to identify genes (and gene products) – "targets" - that were critical to disease
  - and then develop drugs that would act on those targets using structure based design (SBD)
  - not so hit-n-miss – so risks are reduced

Our PCSK9 program comes from this more modern genomic and SBD approach

https://www.cnbc.com/2015/12/10/unlocking-my-genome-was-it-worth-it.html

Genomics and hypercholesterolemia

2003 – enter PCSK9 (Proprotein convertase subtilisin/kexin type 9)

- the PCSK9 gene is associated with increased risk of coronary artery disease *
- the PCSK9 gene produces a protein (PCSK9) that is produced by liver cells and enters the blood to help regulate LDL cholesterol levels
- a gain-of-function mutation in PCSK9 causes genetic (*familial*) hypercholesterolemia *
- humans with an absence of PCSK9 (or loss of function mutations) are healthy AND have significantly reduced LDL cholesterol levels AND a "***strikingly reduced frequency of reduced coronary heart disease***" *

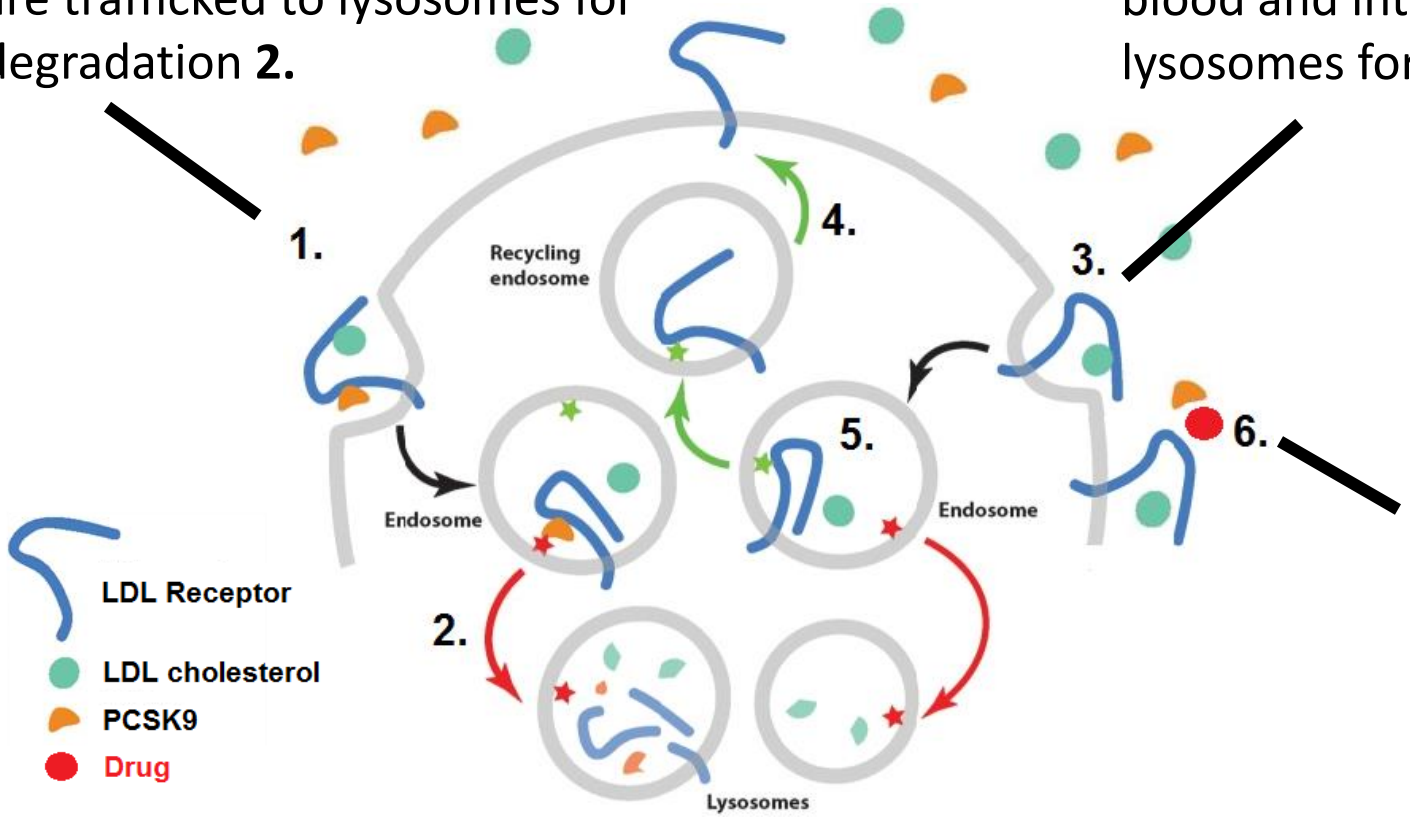
Our PCSK9i program comes from understanding the importance of PCSK9 in this disease and the expected safety profile for a PCSK9i drug

* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2386899/

LDL receptor, LDL cholesterol and PCSK9

1. With PCSK9 bound to the LDL Receptor, there are less LDL Receptors to traffic LDL cholesterol out of the blood and into the cell – because more of the LDL Receptors are trafficked to lysosomes for degradation **2.**

3. Without PCSK9, more of the LDL Receptors traffic back to the cell membrane **4.** ready to shuttle more LDL cholesterol out of the blood and into the cell and then to lysosomes for degradation **5.**



6. Even if PCSK9 is present, a drug can inhibit PCSK9 binding to LDL Receptor so that more LDL Receptors shuttle more LDL cholesterol out of the blood and into the cell **3.**

Adapted from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2386899/figure/fig1

What we are doing

- Next-generation inhibition of PCSK9
  - genomics and the success of the existing biologic PCSK9 inhibitors tells us that PCSK9 is a good “target” i.e. something to inhibit to treat atherosclerosis and vascular disease
  - oral drugs are much more acceptable to patients and cost-effective for patients and payers
  - some experts think that small molecules (i.e. those that are orally available as a tablet taken daily) cannot effectively inhibit the PCSK9-LDL-Receptor interaction *

Small-molecule surprises

Pfizer’s work on a small molecule that targets PCSK9 meanwhile generated fascinating new insights into the basic biology of ribosomal processing.

The appeal of a small-molecule inhibitor of PCSK9 is clear, given the potential for oral pills instead of injectable biologics. But drug developers have struggled to find small molecules that can block the large, shallow protein–protein interaction that PCSK9 forms with LDLR. Even when Pfizer did find a peptide that could block the interaction, it turned out to be too bulky for oral administration (*Chem. Biol.* **21**, 284–294; 2014).

* Nature Reviews Drug Discovery Published online 28 Apr 2017; doi:10.1038/nrd.2017.83

What we are doing

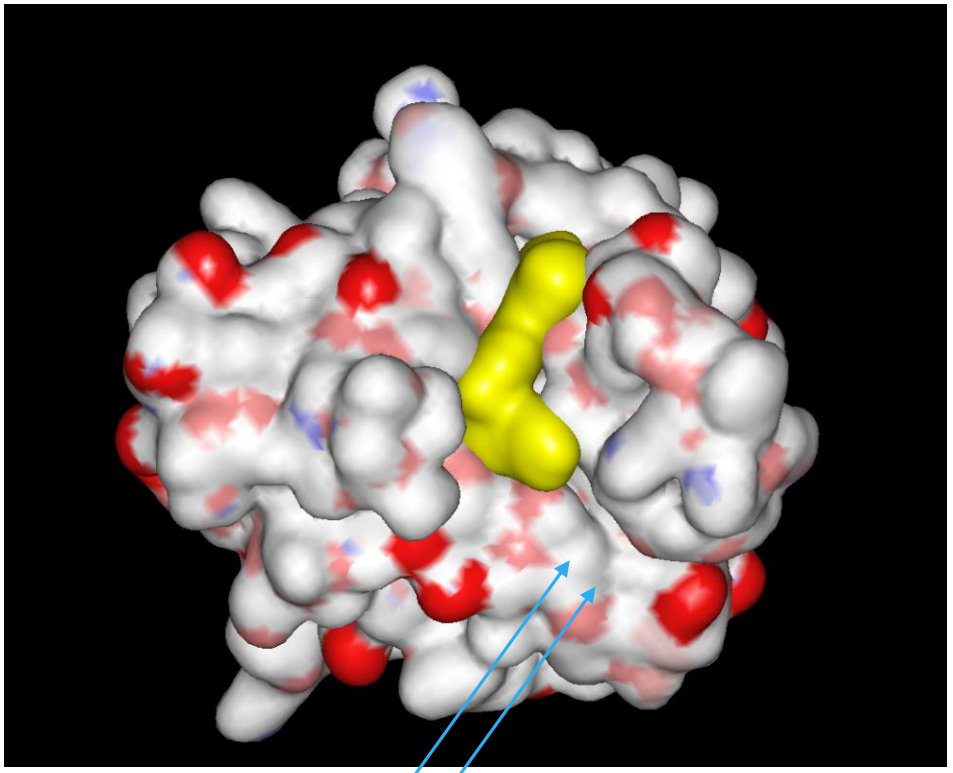
- Next-generation inhibition of PCSK9

Cardio Therapeutics has shown that a small molecule from structure based design (e.g. ALT-30) can indeed effectively inhibit the PCSK9-LDL-Receptor interaction in *in vitro* assays and in-silico screening

Model of PCSK9 (some residues omitted for clarity) with surface plot (charge)

Groove filled with a computational prototype compound (shown in yellow)

✓ It is possible to use a small molecule to inhibit PCSK9 – LDL-R binding



Surface for LDL-R interaction

Courtesy H. Treutlein, J. Zeng, Computist Bio-Nanotech

Who we are

Dr Ian Dixon

Director and Founder of Altnia Group

- Co-inventor of Cardio Therapeutics Pty Ltd PCSK9 technology
- PhD in Biomedical engineering from Monash University
- MBA and Engineering experience
- Director of Noxopharm (ASX-NOX) a listed clinical-stage anticancer company
- Founder of Cynata (ASX-CYP) – a clinical-stage stem cell company now worth ~$70m and partnered with Fuji Film regenerative medicine company
- Co-inventor of ATM-3507 anticancer drug
- Founder and CEO of Exopharm Pty Ltd (www.exopharm.com)

Other members of the team

Person	Key roles	Relationship or affiliation
Dr Jim Palmer	Medicinal chemistry	Consultant
Dr Herbert Treutlein *	Structure-based and fragment-based drug design tools based on their MFMD technology	Sanoosa www.sanoosa.com
Dr Jun Zeng *	Structure-based and fragment-based drug design tools based on their MFMD technology	MedChemSoft www.medchemsoft.com & saltlightpharma.com.au
Dr Ian James	Medicinal chemistry	Consultant
Dr Craig Morton	Structural biology	Consultant
Chempartner (Shanghai, China)	Drug testing	Contractor
Jubilant Biosys (Uttar Pradesh, India)	Drug synthesis	Contractor

* Also as co-founders of Okedro Pty Ltd and Cardio Therapeutics Pty Ltd and experts in structure-based drug discovery

How - The pathway to our PCSK9i as a drug

Further rounds of synthesis and testing

Animal testing of compounds for efficacy and safety

Oral availability of lead compound

Preclinical candidate selection

Manufacture GMP-grade drug

Extensive preclinical safety and efficacy testing in two species

Preparation for Phase I clinical trials

Approval to run clinical trial

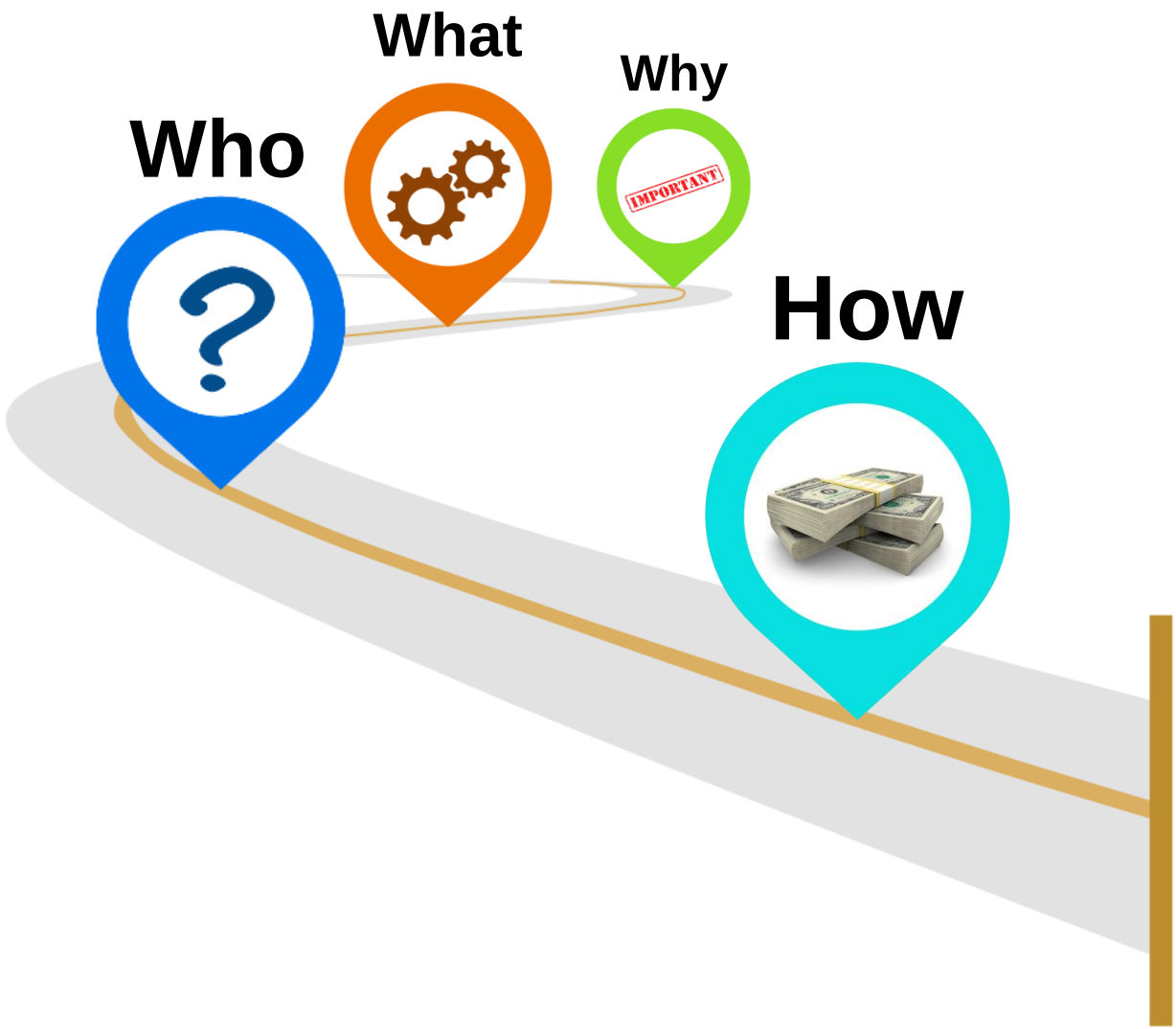
Phase I

Phase IIa

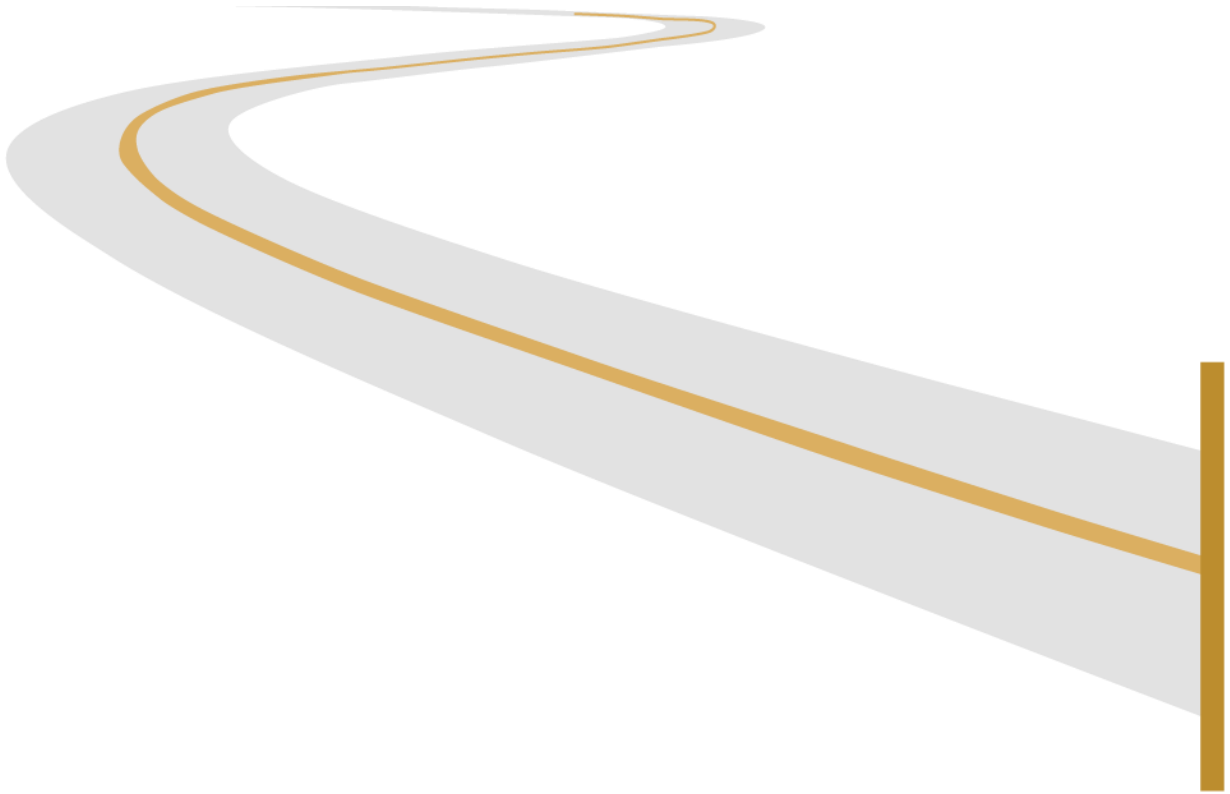
Phase IIb

Phase III

The PCSK9 story outline



An important & valuable new treatment for atherosclerosis and cardiovascular disease



Thank you for
your attention