Pain Cloud® - A Novel in-silico Network Biology Methodology to Develop Personalized Analgesics®

Mark J. Field MSc PhD, eptivA Therapeutics Ltd, Oxford OX33 1TD, UK

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INTRODUCTION

It is estimated that a novel analgesic only has a 1% chance of success in clinical development(7). One of the major reasons for very high attrition rate is a lack of target validation for new analgesic mechanisms and difficulty in linking targets to the optimal patient groups(4).

During the early development of analgesics, animal models or cell-cultures are often used. These might give valuable insights into preclinical biological mechanisms underlying pain, but there is limited evidence they provide target validation for these mechanisms in humans. Development costs remain high and clinical trials continue in the same patient groups rather than those most relevant for the research target. Efficient target validation is difficult as systematic use of human tissue has not been implemented, current approaches to translational research are expensive and labor intensive with a focus often on the specific target instead of the modulation of molecular pathways(4).

Recent advances in high-throughput omic technologies has generated a huge wealth of data that is made available in over 1600 molecular biology databases(5). These data enable in-silico network biology which is an established paradigm to understand complex molecular interactions(8).

We have created a novel in-silico Personalized Analgesics® research method for linking protein research targets to over 1000 pain related conditions from our Pain Landscape®. A range of proteins related to pain have been examined and here we show the disease phenotype output including established mechanisms like CGRP(6) and preclinical false positives like SV2a(9) .

METHODS

Our methods have been previously published in our patent 'Platform for identifying novel analgesic therapies (2023) WO2023058000A1[(1)].

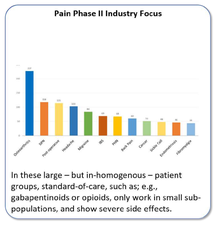
The Pain Cloud® uses a unique algorithm of high quality molecular biology databases which focus on human relevant data. The molecular protein target for any analgesic can be used as the primary input for the algorithm. A range of protein-protein molecular maps are established for the target of interest. The data output from each of the maps are analysed to generate gene ontology pathways likely modulated by the protein interactions. These molecular data are further analysed to identify the disease phenotypes based on the associated biology from the analgesic target.

We have created a novel approach by integrating outputs from these various databases to produce new data on research target to disease links. Our proprietary Pain Landscape® is a collation of 100's of diseases related to pain including rare / orphan conditions which can be utilised to identify target to disease connections.

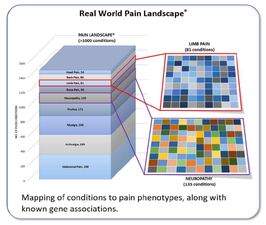
Partnering with digital technology experts Infopoly Ltd, Pain Cloud has been enhanced with a range of software tools to make its application as useful and effective as possible. Its network biology algorithm can be operated automatically, giving access to large data sets from high-quality molecular databases, providing unbiased analyses linking research targets to optimised disease phenotypes.

THE PAIN LANDSCAPE®

Up to now, analgesics clinical development has focused only on a limited number of **~10 pain diseases** with regulatory pathway – our **Pain Landscape®** highlights **over 1,000 conditions** associated with chronic pain.



In these large – but in-homogenous – patient groups, standard-of-care, such as; e.g., gabapentinoids or opioids, only work in small sub-populations, and show severe side effects.

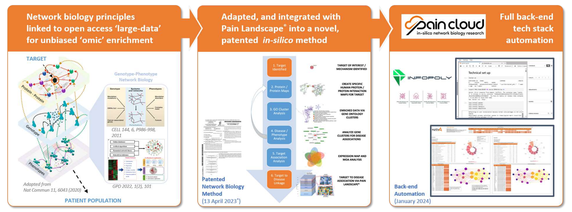


Mapping of conditions to pain phenotypes, along with known gene associations.

Data in left panel are from clinicaltrials.gov search for phase II industry sponsored trials in pain. Data in the right panel depict the 'real world' pain landscape® where we have compiled a database with over 1000 conditions through phenotypic research association. The database contains disease with a phenotypic link to pain along with known gene associations to the diseases

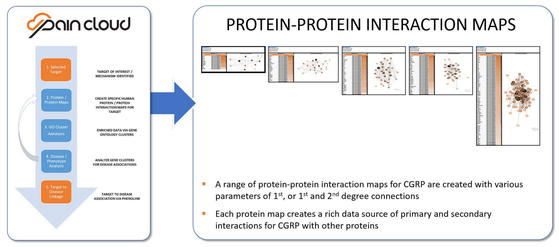
RESULTS

PROPRIETARY PAINCLOUD® TECHNOLOGY PLATFORM



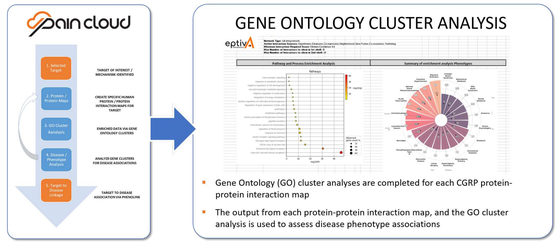
* ... publish date (priority date 8 October 2021)

EXAMPLE OUTPUT CGRP /1



- A range of protein-protein interaction maps for CGRP are created with various parameters of 1st, or 1st and 2nd degree connections
- Each protein map creates a rich data source of primary and secondary interactions for CGRP with other proteins

EXAMPLE OUTPUT CGRP /2



- Gene Ontology (GO) cluster analyses are completed for each CGRP protein-protein interaction map
- The output from each protein-protein interaction map, and the GO cluster analysis is used to assess disease phenotype associations

Top panel represents a graphical overview of network biology concept and the steps in the Pain Cloud methodology. **Middle panel** is a representation of protein – protein interaction maps. **Bottom panel** is a representation of gene ontology and phenotype outputs for one protein – protein interaction map.

SUMMARY OUTPUT CGRP

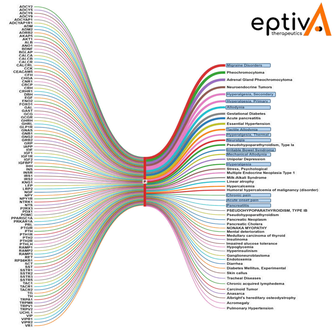
APPROVED MEDICINE

Research on CGRP protein / protein mapping established various disease associations;

- The strongest disease association was for migraine seen across all parameters and is an indication validated in the clinic,
- Associations to various other pain conditions/phenotypes were identified,
- Associations to non-pain diseases with known links to CGRP were also observed.

These data support the network biology approach to identify target to disease links.

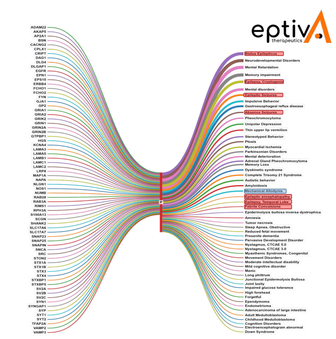
Strong phenotype links to Migraine / Pain



SUMMARY OUTPUT SV2A

PRECLINICAL FALSE POSITIVE

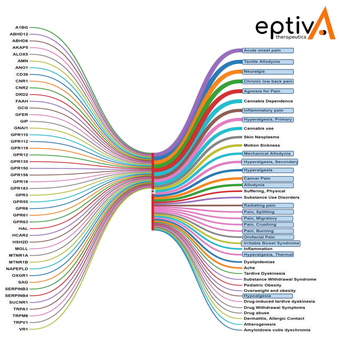
- The synaptic vesicle protein SV2A is the brain binding site of levetiracetam (Keppra), an established antiepileptic drug
- Preclinical data demonstrated evidence of efficacy for SV2a compounds in neuropathic pain models
- The latest systematic review data find no supporting evidence for efficacy in the clinic
- **Strong phenotype links to Epilepsy**
- **But no strong phenotypic links to diseases associated with Pain**



SUMMARY OUTPUT GPR18

NOVEL RESEARCH TARGET

- Orphan G protein-coupled receptors (GPCRs) comprise ~25% of the targetable GPCR space
- Despite their pharmaco-therapeutic potential, they remain understudied, owing to difficulties in interrogating their physiological roles
- We identified a novel strong link for GPR18 to a range of pain conditions, including the clinical pain patient group of radiculopathy
- **Multiple strong phenotype links to Pain**



Example summary output for various research target inputs. Top panel Output for existing medicine mechanism CGRP. Middle panel Output for preclinical false positive mechanism SV2a. Bottom panel Output for novel research target GPR18.

CONCLUSION

To mitigate the challenges posed by traditional pain research and development we have established the Pain Cloud® platform using the Personalized Analgesics® in-silico network biology research to help link targets to disease.

We show that the platform can correctly identify the pain phenotypes associated with the licensed CGRP analgesics, including migraine. The platform also identifies very limited analgesic phenotypes for the SV2a protein. This was a target that demonstrated preclinical efficacy in pain models but failed in clinical development[(2)] .Interestingly, there were strong phenotype links to epilepsy for which this mechanism has established clinical efficacy. Additionally, the platform identified multiple analgesic phenotypes for the orphan GPCR protein GPR18 for which there are limited published data[(3)].

These data highlight the utility of in-silico methodology in linking analgesic research targets to the optimal patient population. The platform can generate patient selection criteria and/or identify a subset of patients that would be suitable for a clinical trial related to the selected therapeutic compound and the one or more identified pain phenotypes/conditions. Pain Cloud® is the first precision medicine approach to pain with the aim of creating more effective treatments and increasing clinical development success.

PAINCLOUD® VALIDATION

We have validated the algorithm with various mechanisms including;

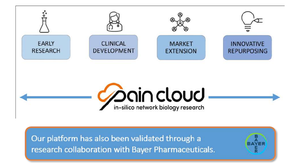
FDA approved pain mechanisms
- NSAIDs (PTGS2)
- Opioids (OPRM1)
- Gabapentinoids (CACNA2D1)
- Capsaicin (TRPV1)
- SNRIs (SLC6A2 / SLC6A4)
- CGRP (CALCA)

Optimal patient groups for known targets; e.g.,
- TRPV3
- VDR

Optimal patient groups for novel targets; e.g.,
- GPR18
- GPR55

Preclinical false positives; e.g.,
- FAAH
- SV2A

Multiple proteins; inherited pain insensitivity patient
- DKK1, GABBR2, BDNF, WNT5B, WNT16, ACKR3, SERPINF1, SFRP2



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