



Introduction to Intellomx Q2 2024

Our Mission



“A selective high-quality molecule will never become a medicine if it is modulating the wrong target. This is why target selection is the most important decision we make in research.”



*Mene Pangalos,
AstraZeneca*

Deploying AI and ML to extract biological knowledge from OMICS data, identifying causal drivers of disease and expediting the biomarker and drug discovery processes.

Our USP



"We're on an unsustainable path, where the cost of drug development is growing enormously, as well as costs of new medicines. We need to ...make the entire process less costly and more efficient. Otherwise we won't continue to realize the practical benefits of advances in science, in the form of new and better medicines."

Scott Gottlieb,
FDA 2017-19



- Extensively validated proprietary processes and algorithms
- Algorithm findings have been validated *In vitro*
- Discovery approach takes weeks rather than years.
- Rapid assessment of millions of molecular combinations
- Human diseased tissue used from hundreds to thousands of cases rather than cell line or animal model data for small numbers of cases

How our AI is different...



- Concordance
 - Driver gene products have to rank high across multiple data sets
 - Results very low probability of false discovery
- Network Inference
 - Strength of driver assigned based on the degree of network integration NOT expression levels
 - Approach allows us to assign biological responsibility for disease based on connections not absolute levels

Revealing Causality...



"A selective high-quality molecule will never become a medicine if it is modulating the wrong target. This is why target selection is the most important decision we make in research."

Intellomx discovers the biological targets that drive disease.



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Intellomx discovers the biological targets that drive disease.

We use proprietary Artificial Neural Network (ANN) technologies to identify the most important drivers of disease v healthy

Rank	Gene ID	Influence
1	IO:01	-17.245
2	IO:02	-11.001
3	IO:03	-10.286
n	IO:nn	+22.585

Multiple databases
Thousands of patients
21,000 RNAseq transcripts
50 million models/hr

Using ANN and systems biology to identify most influential drivers of disease, prioritised according to level of influence between disease and healthy. Targets are examined at molecular pathway level.

Revealing Causality...



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1	IO:01	-17.245
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...		
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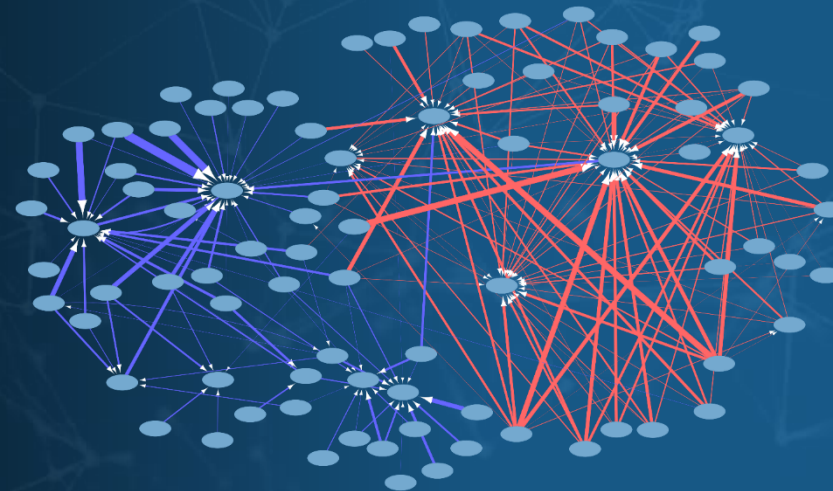
Drivers of disease v healthy



Disease pathway map

Intellomx discovers the biological targets that drive disease.

We map the key drivers of the pathway, creating the first complete pathway maps for each disease under study



Data are represented in Cytoscape maps, showing disease pathways.

Indications include nodes, direction of influence, degree of influence and network effects for each node.

Revealing Causality...



Rank	Gene ID	Influence
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...		
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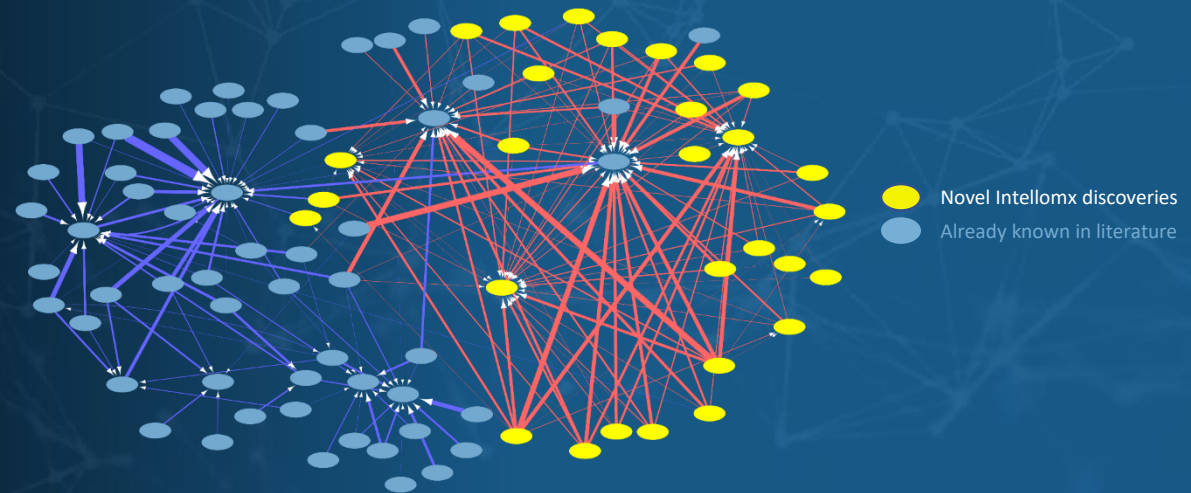
Drivers of disease v healthy



Disease pathway map

Intellomx discovers the biological targets that drive disease.

We compare results to knowledge in the literature to differentiate the novel biological targets from the known



Our AIML approach



"People always ask me where our data comes from, often referencing their own early bioinformatics training and a prejudice about the issue of data quality. Modern RNAseq technologies and our unique ability to eliminate data bias using in-house statistical methods has changed all that."



Graham Ball
CSO & co-founder

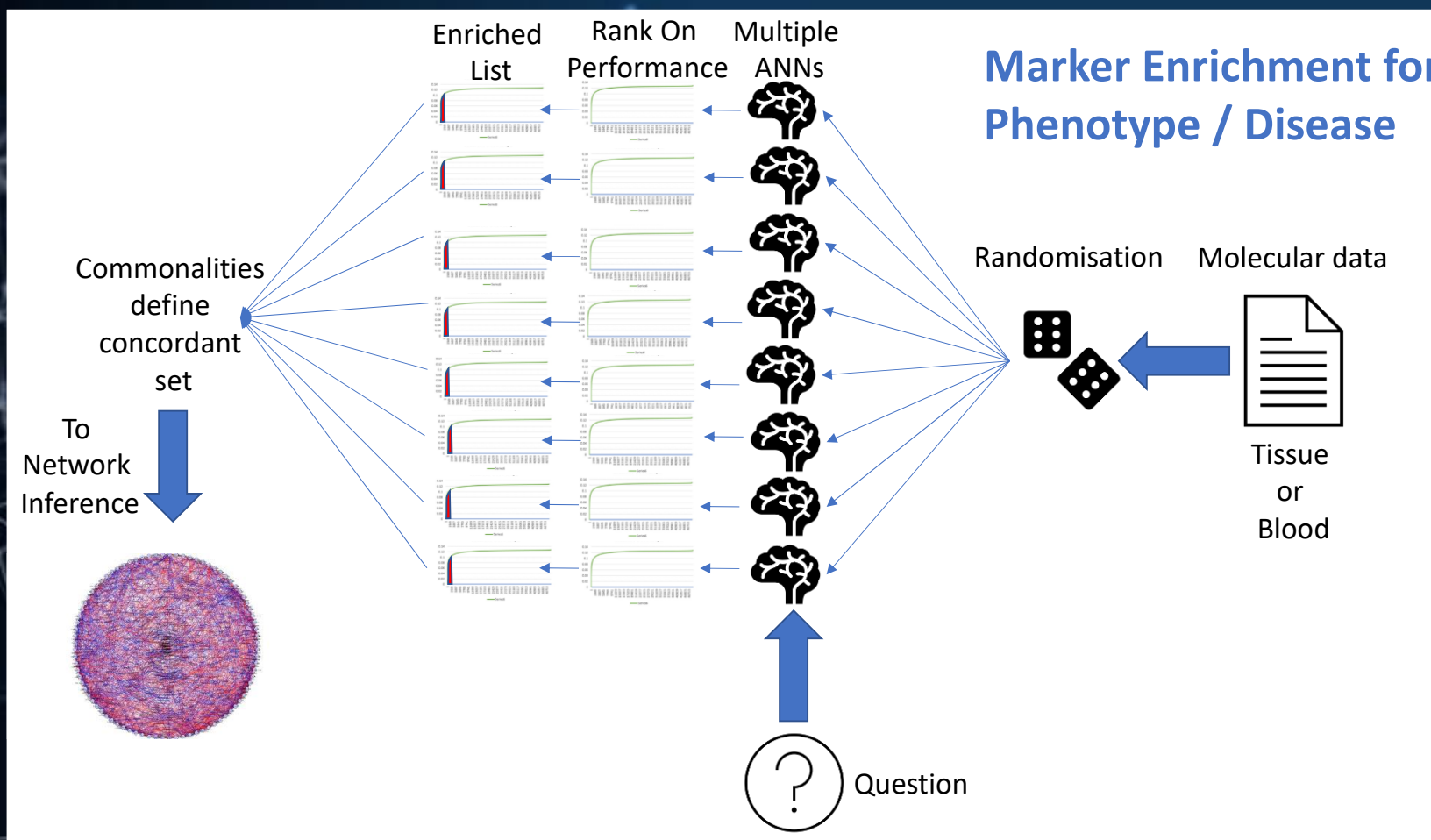
- Unique concordance-based approach deploys 5 layers of validation across multiple datasets.
- Unique pathway miner approach fills gaps in pathway knowledge based on evidence from the whole transcriptome
- Unique network inference approach to understand the amount of influence of each molecule in a pathway
- Unique stability-based approach identifies level of dysregulation of each molecule in the pathway
- Unique digital twin approach builds comparator pathway models for healthy state in tissue of interest and in off target tissues.

Intellomx Distiller



Our proprietary Distiller platform looks for concordant molecules over hundreds of different views of multiple data sets.

This eliminates the risk of false discovery facilitating robust evidence-based discovery from large scale omics data.



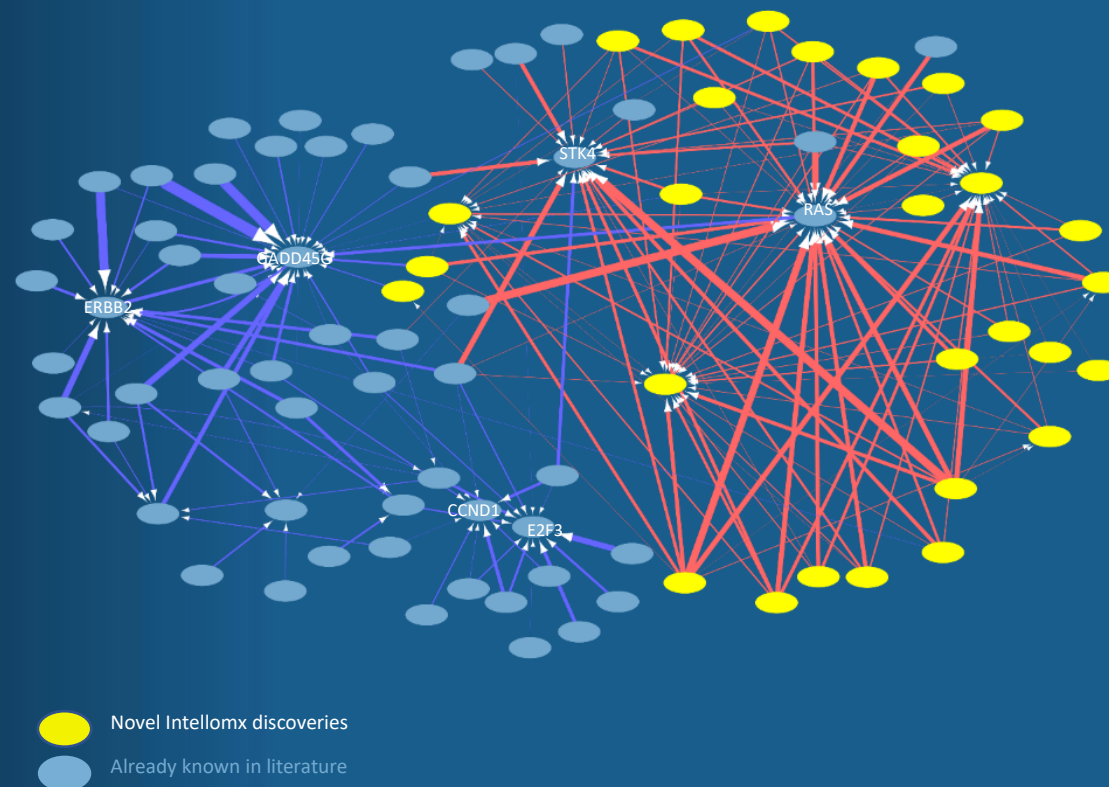
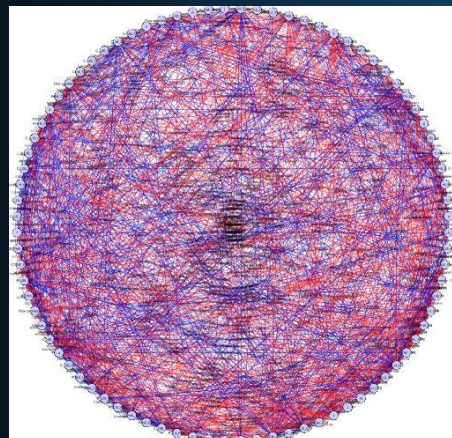
Intellomx Driver



Our driver discovery process models the interactions between molecules identifying the most connected and influential molecules in a system.

Our discovery doesn't just rely on fold change and p values but gets to the core of the molecular processes that drive a biological system.

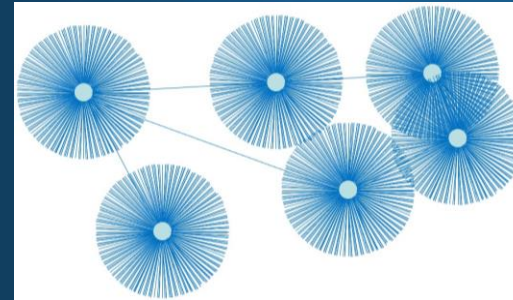
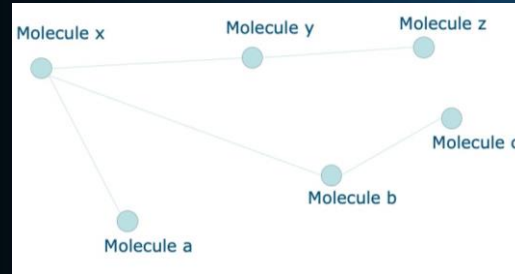
This approach builds a model of the interaction space which can be interrogated to discover the most influential molecular features for drug target discovery and the level of dysregulation of a molecular feature.



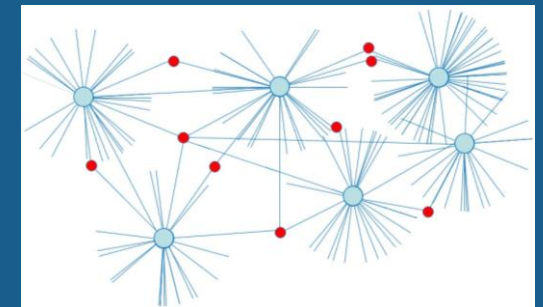
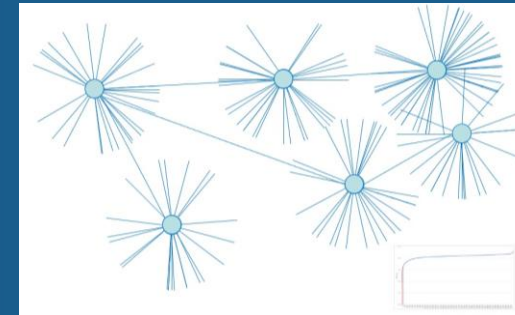
Intellomx Pathway Miner



Intellomx pathway miner uses a molecular pathway or gene list as a framework. Deploying the principles of Intellomx Distiller we can discover new evidence-based features.



The approach mines the whole transcriptome to identify new members or associations with the pathway based on evidence from the whole transcriptome.

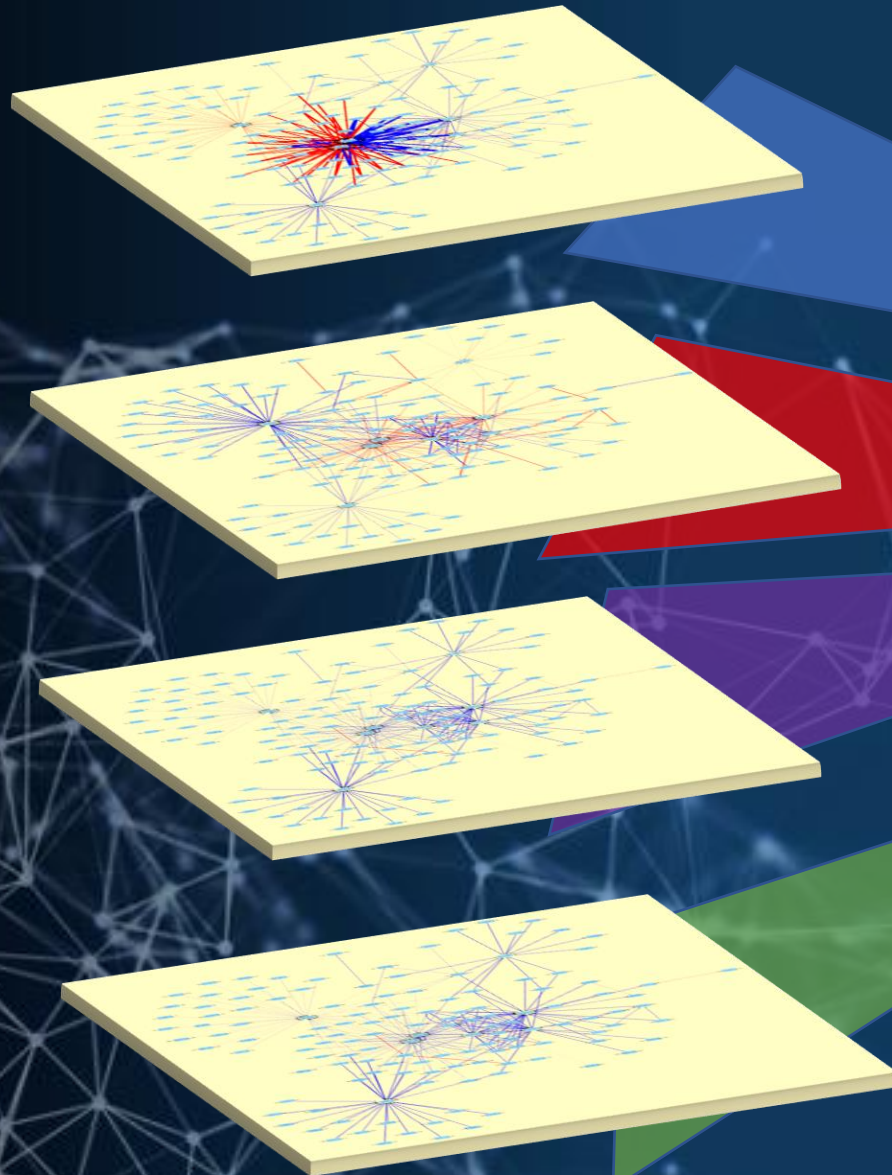


Digital Twin



“The Intellomx Digital Twin gives us the opportunity to test drugs in development in a human model without risk, giving a clear indication of off-target toxicity effects:

- We can now **predict the specific off-target effects for any molecule under study** by applying our pathway analysis regarding the brain, kidney, skin, blood, liver and other organs.
- In turn this enables us to prioritise molecules for development, eliminating up to 90% of projects that would fail due to toxicity in later, high-cost stages.



Case Study: Lung Cancer (KRAS)

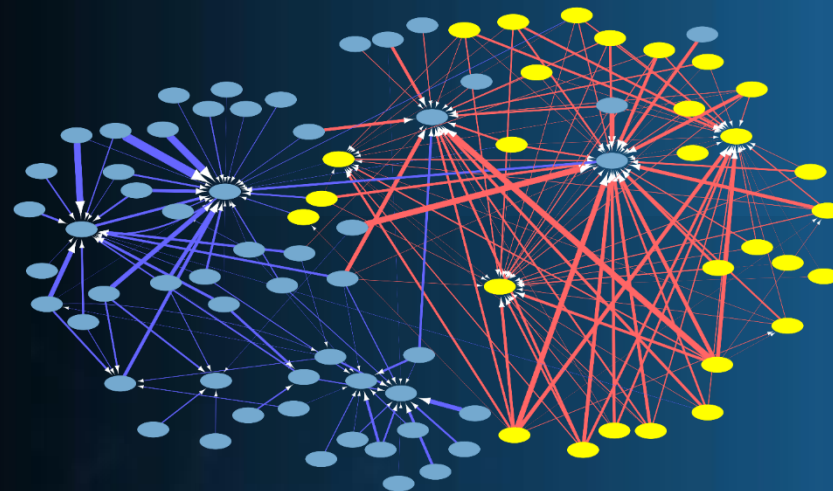


ARCTORIS



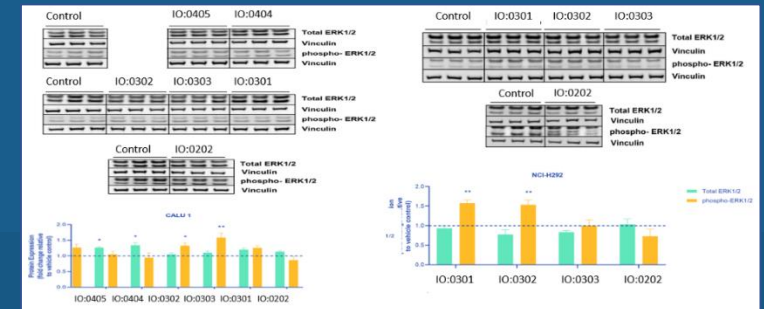
Project supported by Innovate Grant 2021. Intelligent OMICS led the program, supported by subcontractors Medicines Discovery Catapult and cell-line robotics company Arctoris Ltd.

- Assessment of KRAS/MEKK inhibition in Lung Cancer
- Top 200 drivers evaluated via analysis of 9 lung cancer datasets, generating 30 novel targets in KRAS (22 in MEKK)
Results presented in Cytoscape ...



● Novel Intellomx discoveries
● Already known in literature

+



Validation:

WP 1.1 siRNA Screen: phenotypic outcome 24, 48, 72 and 96h
WP 1.2 Pathway Analysis screen: siRNA transfection. Target depletion confirmed
WP 2 Compound Screen: siRNA transfection. Target depletion confirmed

Results validated in Wild Type and Mutated cell lines by Arctoris

Lung Cancer (KRAS)

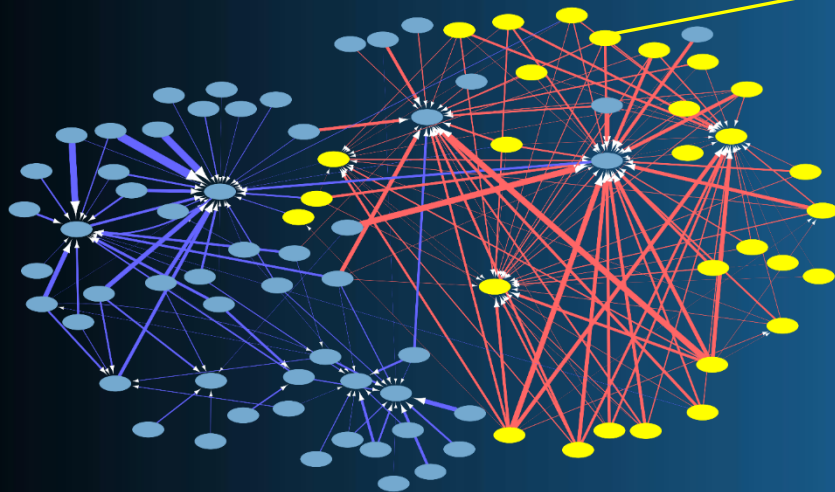


“Our system validated the targets and then tested drugs against those targets. Results were clear – the targets identified by Intelligent OMICS are indeed important, previously unknown targets in lung cancer and the novel drugs identified by the team modulate those targets, all as predicted by the AI.”



Martin Bittner
CEO

3 biological targets and 7 molecules prioritized for development and partnering



IO:03 KRAS inhibitor

- IO:0301 Small molecule wild type
- IO:0302 Small molecule wild type
- IO:0303 Small molecule wild type+G12C
- IO:0304 Monoclonal wild type+G12C

IO:04 KRAS/MEKK inhibitor

- IO:0404 Small molecule G12C
- IO:0405 Small molecule G12C

IO:02 MEKK inhibitor

- IO:0202 Small molecule wild type+G12C

Differentiation



Intellomx

Other AI

Traditional
R&D

New source of
biological targets



Fast



de novo research



Human data only



Intellomx Digital Twin



Reduced animal trials



Improved resource
use + sustainability



Key papers + illustrations:



Articles

Lancet oncology

Supplementary data available on request

SPAG5 as a prognostic biomarker and chemotherapy sensitivity predictor in breast cancer: a retrospective, integrated genomic, transcriptomic, and protein analysis

Tarek M A Abdel-Fattah¹, Devika Agrawal¹, Dong Wu Lu¹, Rodin Khorrami¹, Oscar M Novels¹, Karen Liu¹, Bing Xu¹, Paul M Mowday¹, Andrew H Green¹, Alan Chubbey¹, Robert Evers¹, Corin Galvin¹, Ian O'Dea¹, Graham R Ball², Stephen Y T Chan³

Summary Identification of prognostic markers and predictive biomarkers has been recommended for guiding the choice of systemic treatment.

REGULAR ARTICLES

Blood advances

A parsimonious 3-gene signature predicts clinical outcomes in an acute myeloid leukemia multicohort study

Sarah Wagner¹, Jayakumar Vadakekottu¹, Sarah K. Tasian², Hadi Altamr³, Martin Bornhäuser⁴, A. Graham Pocock¹, Graham R. Ball¹, and Sergio Restallá⁵

Key Points

- Machine-learning approaches identified a parsimonious 3-gene expression signature that predicts risk in newly diagnosed AML.
- The 3-gene PI could be used to refine the accuracy of patient stratification and outcome prediction in routine clinical practice.

Acute myeloid leukemia (AML) is a genetically heterogeneous hematological malignancy with variable responses to chemotherapy. Although recurring cytogenetic abnormalities and gene mutations are important predictors of outcome, 50% to 70% of AML harbor normal or risk-indefinite karyotypes. Therefore, identifying more effective biomarkers predictive of treatment success and failure is essential for informing tailored therapeutic decisions. We applied an artificial neural network (ANN)-based machine learning approach to a publicly available data set for a discovery cohort of 593 adults with nonpromyelocytic AML. ANN analysis identified a parsimonious 3-gene expression signature comprising *CALCR1*, *CD109*, and *LSP1*, which was predictive of event-free survival (EFS) and overall survival (OS). We computed a prognostic index (PI) using normalized gene-expression levels and β -values from subsequently created Cox proportional hazards models, coupled with clinically established prognosticators. Our 3-gene PI separated the adult patients in each European LeukemiaNet cytogenetic risk category into subgroups with different survival probabilities and identified patients with very high-risk features, such as those with a high *WT* and either *FZD3* internal tandem duplication or mutated nucleophosmin 1. The PI remained significantly associated with poor EFS and OS after adjusting for established prognosticators, and its ability to stratify survival was validated in 3 independent adult cohorts ($n = 905$ subjects) and 1 cohort of childhood AML ($n = 145$ subjects). Further, in silico analyses established that AML was the only tumor type among 39 distinct malignancies for which the concomitant upregulation of *CALCR1*, *CD109*, and *LSP1* predicted survival. Therefore, our ANN-derived 3-gene signature refines the accuracy of patient stratification and the potential to significantly improve outcome prediction.

Introduction

Acute myeloid leukemia (AML) is characterized by bone marrow (BM) and tissue infiltration by proliferative clonal abnormally differentiated cells of hematopoietic origin.¹ Prognosis is largely determined by cytogenetic abnormalities and AML-specific molecular lesions.² Although AML can be cured in 30% to 40% of adult patients aged <60 years with multiagent chemotherapy and often hematopoietic stem cell transplantation (HSCT), chemotherapy disease is common, and relapse represents a major cause of treatment failure.³ Investigation of new molecularly targeted agents for children and adults with high-risk AML remains a high priority.^{4,5}

frontiers in Oncology

Frontiers in oncology

Comprehending Meningioma Signaling Cascades Using Multiscale Modeling

Yuan Fan, Clyn Bradley¹, Kevin Pyke, Graham Ball, Chungui Lu, Rupert Fry, Alexandra Marshall¹, Subhalaj Jayasuta, Charles Baxter, Rik van Wijk, Laurie Boyden, Rebecca Cade, Natalie H. Chapman, Paul D. Fraser, Charlie Hodgman, and Graham B. Seymour²

Plant physiology

Network Inference Analysis Identifies an *APRR2-Like* Gene Linked to Pigment Accumulation in Tomato and Pepper Fruits^{1|10|10A}

Yu Fan, Clyn Bradley¹, Kevin Pyke, Graham Ball, Chungui Lu, Rupert Fry, Alexandra Marshall¹, Subhalaj Jayasuta, Charles Baxter, Rik van Wijk, Laurie Boyden, Rebecca Cade, Natalie H. Chapman, Paul D. Fraser, Charlie Hodgman, and Graham B. Seymour²

Division of Plant and Crop Sciences, University of Nottingham, Sutton Bonington, Loughborough LE12 5RD, United Kingdom (Y.F., G.B., K.P., C.L., R.F., A.M., S.J., N.H.C., C.H., G.B.S.); School of Science and Technology, Nottingham NG11 8NS, United Kingdom (G.B.); Syngenta Seeds, Jealott's Hill International Research Station, Barchin, Berkham RG42 6EY, United Kingdom (C.B.); Syngenta Seeds, F-31790 Saint-Sauver, France (R.v.W.); Syngenta Seeds, Stanton, Minnesota 55018 (L.B.); Syngenta Biotechnology, Research Triangle Park, North Carolina 27709 (R.C.); and School of Biological Sciences, Royal Holloway University of London, Egham Hill, Egham TW20 0EX, United Kingdom (P.D.F.)

Carotenoids represent some of the most important secondary metabolites in the human diet, and tomato (*Solanum lycopersicon*) is a rich source of these health-promoting compounds. In this work, a novel and trait-related regulator of pigment accumulation in tomato has been identified by artificial neural network inference analysis and is function validated in transgenic plants. A tomato fruit gene regulatory network was generated using artificial neural network inference analysis and transcription factor gene expression profiles derived from fruits sampled at various points during development and ripening. One of the transcription factor gene expression profiles with a sequence related to an Arabidopsis (*Arabidopsis thaliana*) *ARABIDOPSIS FLEUDO REPLICASE REGULATORY-LIKE* gene (*APRR2-Like*) was up-regulated at the breaker stage in wild-type tomato fruits and, when overexpressed in transgenic lines, increased plastid number, area, and pigment content, enhancing the levels of chlorophyll in immature stripe fruits and carotenoids in red ripe fruits. Analysis of the transcriptome of transgenic lines overexpressing the tomato *APRR2-Like* gene revealed up-regulation of several up-regulated genes in the ripening process, providing a link between the expression of this tomato gene and the ripening process. A putative ortholog of the tomato *APRR2-Like* gene in sweet pepper (*Capiscum annuum*) was associated with pigment accumulation in fruit tissues. We conclude that the function of this gene is conserved across taxa and that it encodes a protein that has an important role in ripening.

Tomato (*Solanum lycopersicon*) is a climacteric fruit for extending ripening in fleshy fruits because of the epistatic genetic and molecular resources that are available, including well-characterized mapping populations (Leppan et al., 2007), numerous single-gene mutants, routine transformation, and a fully annotated genome sequence (Tomato Genome Consortium, 2012). The repertoire of well-characterized mutations in tomato has permitted the identification of genes that encode proteins that govern the ripening process. These have included *Never Ripen 1* (*NR1*), *FRUITING INHIBITOR 1* (*FRIN1*), *non-ripening 1* (*nor*), and *Colorless nonripening 1* (*Cnr*). Mutations at these loci can completely abolish normal ripening (Lanahan et al., 1994; Vrebalov et al., 2002; Manning et al., 2006). The *NR*, *RIN*, *CNR*, and *CNR* gene products, along with those from tomato *Hd-Zip* (*homodimer protein 1*) (*HdHP1*), *Tomato AGAMOUS-LIKE1* (*TAGL1*), *APETALA2* (*AP2*), Liu et al., 2008; Iken et al., 2009; Vrebalov et al., 2009; Chung et al., 2010; Karlova et al., 2011), and others govern the onset and progression of the ripening. Despite a growing understanding of this high-level regulatory network, the links to hormonal cues, plastid signals, and downstream effectors mediating alterations in color, texture, and flavor are still poorly understood.

10A This work was supported by the Biotechnology and Biological Sciences Research Council ESB-Link program (grant nos. BB/P00549/1 to C.H. and G.B.S. and BB/P00550/1 to P.D.F.), the BBSRC NET TomQML program (grant nos. BB/C00291X to G.B.S. and BB/R02808/1 to P.D.F.), and the TomNet project (grant nos. BB/J08407/1 to P.D.F. and BB/J08991 to G.B.S.). All awards were in collaboration with Syngenta Seeds.

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^{10B} Open Access articles can be viewed online without subscription.

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frontiers in Immunology

Frontiers in biology

Development of a Bioinformatics Framework for Identification and Validation of Genomic Biomarkers

Tarek M. A. Abdel-Fattah¹, Devika Agrawal¹, Dong Wu Lu¹, Rodin Khorrami¹, Oscar M. Novels¹, Karen Liu¹, Bing Xu¹, Paul M. Mowday¹, Andrew H. Green¹, Alan Chubbey¹, Robert Evers¹, Corin Galvin¹, Ian O'Dea¹, Graham R. Ball², Stephen Y. T. Chan³

JAMA Network Open

Jama network

Original Investigation | Oncology

Association of Sperm-Associated Antigen 5 and Treatment Response in Patients With Estrogen Receptor-Positive Breast Cancer

Tarek M. A. Abdel-Fattah, PhD, Graham R. Ball, PhD, Paul U. Thangavelu, PhD, Lynne E. Reid, PhD, Amy E. McCart Reed, PhD, Jodi M. Szarovs, PhD, Pascal H. G. Duff, PhD, Peter J. Simpson, PhD, Sarah L. Lakhani, MD, Lorne Torrey, PhD, Balakrishna G. Prasad, PhD, Paul M. Mousley, ESC (Hon), Andrew K. Green, PhD, Alan G. Pocock, PhD, Corin Galvin, PhD, Ian O'Dea, PhD, Stephen Y. T. Chan, MD

Abstract

IMPORTANCE: There is no proven test that can guide the optimal treatment, either endocrine therapy or chemotherapy, for estrogen receptor-positive breast cancer.

OBJECTIVE: To investigate the associations of sperm-associated antigen 5 (SPAG5) transcript and SPAG5 protein expressions with treatment response in systemic therapy for estrogen receptor-positive breast cancer.

DESIGN, SETTINGS, AND PARTICIPANTS: This retrospective cohort study included patients with estrogen receptor-positive breast cancer who received 5 years of adjuvant endocrine therapy with or without neoadjuvant anthracycline-based combination chemotherapy (NACT) derived from 11 cohorts from December 1, 1986, to November 28, 2019. The associations of SPAG5 transcript and SPAG5 protein expression with pathological complete response to NACT were evaluated, as was the association of SPAG5 mRNA expression with response to neoadjuvant endocrine therapy. The association of SPAG5 mRNA expression with SPAG5 transcript or SPAG5 protein expressions were analyzed. Data were analyzed from September 9, 2015, to November 28, 2019.

MAIN RESULTS AND MEASURES: The primary outcomes were breast cancer-specific survival, distant relapse-free survival, pathological complete response, and clinical response. Outcomes were examined using Kaplan-Meier, multivariable logistic, and Cox regression models.

RESULTS: This study included 12 720 women aged 24 to 78 years (mean [SD] age, 58.46 [12.45] years) with estrogen receptor-positive breast cancer, including 1073 women with SPAG5 transcript expression and 361 women with SPAG5 protein expression of locally advanced disease-stage IIIA through IIIC. Women with SPAG5 transcript and SPAG5 protein expressions achieved higher pathological complete response compared with those without SPAG5 transcript or SPAG5 protein expressions (transcript: odds ratio, 2.45 [95% CI, 1.71-3.51]; $P < .001$; protein: odds ratio, 2.32 [95% CI, 1.33-4.22]; $P < .001$). Adding adjuvant anthracycline chemotherapy to adjuvant endocrine therapy for SPAG5 mRNA expression in estrogen receptor-positive breast cancer was associated with prolonged 5-year distant relapse-free survival in patients without lymph node involvement (hazard ratio, 0.34 [95% CI, 0.14-0.87]; $P = .033$) and patients with lymph node involvement (hazard ratio, 0.35 [95% CI, 0.18-0.68]; $P = .002$) compared with receiving 5-year endocrine therapy alone. Mean OS/SPAG5 transcript was found to be downregulated after 2 weeks of neoadjuvant endocrine therapy compared with pretreatment levels in 68 of 92 patients (74%) (0.21 [0.18] vs 0.34 [0.24]; $P < .001$).

Supplemental content: Author affiliations and article information are listed at the end of this article.

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OBN supporting and bringing together the UK's life sciences companies, corporate partners and investors

CONNECT

DDI & drug

Intelligent OMICS, UKRI, Innovate UK, CATAPULT Medicines Discovery, ARCTORIS

Conquering KRAS!

The AI drug discovery revolution that is here to stay

Intelligent OMICS is delighted to announce successful completion of its recent Innovate UK grant program, in collaboration with the Medicines Discovery Catapult (MDC) and Arctoris Limited.

5 key conclusions:

- Application in oncology identifies novel KRAS-inhibiting drugs for lung cancer, one of which is even effective regardless of KRAS mutation.
- AI-driven drug discovery is at last proven, and ready for application across multiple diseases.
- The AI approach discovers new drugs because it focuses on the drivers or causes of the disease state, rather than focusing on the symptoms or effects of a disease state.
- The evidence-based analysis produces original results, without reliance on prior hypotheses or literature, allowing creation and control of new intellectual Property.
- AI discovery methods can achieve greater than 90% reduction in cancer footprint compared to traditional high-throughput screening.

The project, led by Intelligent OMICS and funded by Innovate UK, sought to demonstrate the carbon efficiency of an AI-based drug discovery program compared to traditional pharma methods. The case study used in the project was assessment of Non-Small Cell Lung Cancer – thought to account for over 80% of all lung cancer cases.

Method

The team analysed nine lung cancer datasets from the Intellomx Curated Data Library, using the Intelligent OMICS platform. The datasets include human transcriptomic data plus confirmation of a disease v healthy diagnosis for lung cancer for approximately 2,000 patients. Proprietary AI was used to model the underlying systems biology – first creating a list of the most important genes defining the disease v healthy diagnosis, then modelling the interaction of those genes in a disease pathway map based on the evidence in the data.

"The real benefit of our technology is evident when we compare our results with what is known in the literature," says Intellomx CEO Dr Simon Haworth. "We can immediately spot errors and omissions in pathway maps documented in KEGG. For example, and because our analysis only focuses on the most influential drivers in each pathway we know that any such differences are genuinely important. For our lung cancer work, focussing on EGFR and KRAS, the comparison led us to 8 really exciting new lung cancer targets."

The next step of the process was to validate *in silico* targets in the wet lab, to link validated targets to possible drugs and then to test the impact of those novel drugs on cancer cells.

Subcontractor Arctoris, with its world leading fully automated drug discovery platform and robotic cell line system, provided rapid validation of the targets using knock down analysis on KRAS G12C mutant and KRAS wild type cell lines. Data from Arctoris proved the validity of the targets on

Our Clients



“I love this collaboration already – in under 4 weeks you have provided a clearer picture of [disease] than we have achieved from 4 years of hard work. Let’s move to the next level!”



Philippe Moingeon
Director,
Laboratoire Servier

Corporate contracts

	Dengue vaccine		Sepsis		Sjogren’s, SLE
	TB, Sepsis		Pro-biotic response		
	Cell therapy, Toxicity		AML		
	Sepsis, COPD		Rh Arthritis		Oncology
	Sepsis, Viral infection		Prostate cancer		
	Prostate cancer		Renal cancer		
	Tomato ripening		TB		
	Oncology asset		Autoimmune		

Academic collaborations

	Preeclampsia, resp, renal		Breast cancer		Tuberculosis
	Breast, ovarian		Cell-based therapy		
	Prostate, campylobacter		Melanoma		
	Breast, Sepsis		Melanoma		
	Oncology, diabetes				



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