Information Memorandum



Next Generation AI for Drug Discovery

Pharma's problem, Al's answer

"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, former VP, AstraZeneca





"Artificial intelligence is the key to unlocking the vast potential of novel biological targets, transforming the way we discover new drugs. By intelligently mapping the complexity of biology, AI accelerates the identification of promising targets, enhancing the precision and speed of therapeutic breakthroughs."

Demis Hassabis CEO of Google DeepMind



Executive Summary

Intelligent OMICS

Intellomx is a UK-based firm leveraging innovative AI and machine learning to enhance and de-risk drug discovery and develop precision medicine approaches through precise in silico technologies:

Our USP lies in our capacity to understand the fundamental biology of disease. This insight Biology • allows us to pinpoint the optimum targets and drug candidates, for maximum patient populations. Docking Post target ID and validation, our docking algorithms can identify lead drug candidates for • development. Validation Our findings have been confirmed in human biology and plant physiology, leading to the creation of in-house assets and intellectual property for both Intellomx and its collaborators. Data is no longer a constraint. We harness both public and proprietary information in genomics, Data • proteomics, metabolomics and transcriptomics to discover new targets that influence disease. **Swarm Algorithm** Our algorithms invoke multiple, parallel swarms of analyses rather than compute-resource hungry • deep-models. Swarms are 90% more efficient, minimize risk of false discovery and are explainable. Collaboration Our twin-track business approach features (1) a "fee for service" option, underpinning our internal ۲ research discovery initiatives, and (2) shared IP partnerships. Target ID and docking done, Intellomx is building an integrated model of human disease pathways, The Future captured in the form of the Intellomx Digital Twins - heralding the future in drug discovery.

Intellomx leads the way in this new era of precision drug discovery, utilizing its proprietary AI/ML to identify optimal drug targets and linking those targets to ranked drug candidates – actionable insights for pharmaceutical collaboration.

Solution – Intellomx I³



l ³ -Distiller	Identification of key genes
l ³ -Driver	Identification of key disease drivers
l ³ -Miner	Defining the disease pathway
CARS V	
I ³ -Digital Twin	Anticipating tox liabilities

I³-PilotIdentification of novel Small
Molecules and BiologicsI³-PrecisePanel optimization for diagnostics

The Intellomx I³ toolkits model different aspects of the underlying systems biology of disease, using proprietary Artificial Neural Networks and Machine Learning techniques developed in-house.

The primary tools (Distiller, Driver and Miner) model disease pathways at the molecular level whilst our Digital Twin anticipates toxicity liabilities.

Novel Intellomx discoveriesAlready known in literature

Intellomx I³: Intuitive, Informed, Intelligence

Solution – Intellomx I³

Digital Twin

The Intellomx Digital Twin tests drugs in development in an Algenerated human model without risk, giving a clear indication of offtarget toxicity.

We can thus prioritise molecules for development, eliminating up to 90% of projects that would fail due to toxicity in later, high-cost stages.

In future, a population of Intellomx Digital Twins will enable *in silico* clinical trials.





Solution: I³ for drug discovery/development



Swarm Based AI Approaches





- Trains large numbers of smaller less deep Neural Network Models
- Each model takes a different view of the data or addresses a different part of the problem
- Data presentation allows the whole problem to be represented with overlaps
- Early stopping and regularisation and Monte Carlo cross-validation built in.
- >1000 models run at the same time on different compute units of a GPU
- All of the transcriptome is considered in parts, starting from a single gene product

Our Swarm-Based AI/ML Approach

Intelligent OMICS

- Unique concordance-based approach deploys 5 layers of validation across multiple datasets.
- Unique Swarm ML-based approach increased explainability, reduced false discovery and increased time and energy efficiency
- 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 the level of dysregulation of each molecule in the pathway
- Unique digital twin approach builds comparator pathway models for healthy states in tissues of interest and in off-target tissues.
- Unique Tox twin approach models toxicity and cellular stress response across multiple tissues comparison with pathway models determines the nature of toxicity risk.

Intellomx Pilot – Druggability and Screening



- Incorporates results from I3 to select biological targets of highest relevance.
- Screens biological targets for Druggability based on molecular ontological data.
- Identifies a ranking of small molecules based on ligand-receptor binding; Based on combined ligand, target structural and energetic binding characteristics.
- Screens over 500 million targets.
- Further screening based on ADME characteristics.

Application in Personalized Medicine I³ = Profit



Challenge

My drug failed in clinical trials

My drug is efficacious for a small patient population, making development uneconomic

We need to maximise the patient population in our discovery process

Solution

I³ analysis identifies the target patient group and the companion diagnostic delivers the stratification for trials

I³ identifies the MAXIMUM stratified patient population and/or identifies additional targets and associated drug molecules to complement the existing drug

I³ calculates the stability of each target across the population, enabling selection of the maximum target group

Note: I³ application has been proven in re-analysis of failed trials for major pharma, and in identification of maximum populations for diseases with material patient stratification

Application in Personalized Medicine: Prediction of Drug Response from PDC to Patient

Model Development

AUC response for Compound X in a PDC tissue model.

Drivers of response







In vitro

efficacy



Population of disease cases

Data Types Utilised by Intellomx

- DNA Sequencing and Genomics
 - Point Mutations
 - Copy Number Variation
- Transcriptomic
 - RNASeq
 - scRNASeq
 - Expression array data (post-2012)
 - Nanostring nCounter[®] and GeoMX[®] data
- Proteomic data
 - Mass spectrometry
 - Protein array
- Methylation
- Clinical, outcome, response and phenotypic data
- Integration of MultiOmics data

Case Study: Obesity

- Pathway: GLP1R molecular system In White adipose Tissue, Normal and Obese
- Data Sets: GSExxxxxx: 68 Obese Cases BMI >30; 142 Non-Obese Cases BMI <25
- Entire transcriptome analyzed for associations with GLP1R
- Separate analysis conducted to determine phenotypic drivers of Obesity
- Overlap explored. Key features available for consideration in ranking analysis:
 - Degree of driver influence of a given gene product in the disease network
 - Degree to which the disease network influences a gene product
 - Degree of pathway connectivity
 - Stability of gene product across the population

GLP1 comparison with phenotypic state:

- GLP1R showed low expression in white adipose tissue
- No overlap with the phenotypic state
- Putative obesity-related targets found in white adipose tissue, independent of GLP1R
- Future exploration of other tissues to identify where GLP1R plays a role and the molecular system surrounding it.

Intelligent	
OMICS	

	Gene Function								
	1 winged helix/forkhead transcription factor								
	2 synthase via transamidation and mitochondrial translation								
	3 involved in double-strand break repair								
	4 Enables estrogen receptor binding activity and histone kinase activity								
	5 ubiguitin-protein ligase								
	6 Protein Kinase								
	7 transferase								
	8 viral or transposable ele	ment protein							
	9 PNA binding	Rank family							
4	0 non-recentor series /th	1 actin or actin-binding cytoskeletal protein							
	to hom-receptor serine/ th	2 Zinc Finger protein							
	li nyurolase	3 heterotrimeric G-protein							
1	12 non-motor actin bindin	4 ATP synthase							
1	L3 SNARE protein	5 serine protease							
1	14 DNA topoisomerase	6 Pseudo Gene							
1	15 Has epimerase activity.	7 Transmembrane Protein							
1	L6 scaffold/adaptor protei	8 Tumour supressor gene							
1	17 Pseudogene	9 Transmembrane Protein							
1	18 RNA splicing factor	10 glycosyltransferase							
1	19 scaffold/adaptor protei	11 G-protein coupled receptor							
2	0 Involved in positive reg	12 extracellular matrix protein							
2	1 RNA Binding Protein	15 giycosyltransferase							
	2 Pseudogene	15 transporter							
	23 Mitochondrial Binding (16 ligase							
	ta herebatare	17 dehydrogenase							
1	4 phosphatase	18 Long Intergenic Non-Protein Coding RNA							
-	25 transporter	19 scaffold/adaptor protein							
2	26 RNA metabolism protei	20 non-receptor serine/threonine protein kinase							
2	27 RNA processing factor	21 scaffold/adaptor protein							
2	28 non-receptor serine/th	22 guanyl-nucleotide exchange factor							
2	9 chromosomal structura	23 Protein Phosphotase							
3	80 secondary carrier trans	24 Vesicular Protein							
	AN	25 dehydrogenase							
Ę		26 Aldehyde Dehydrogenase							
		27 secondary carrier transporter							
		28 kinase activator							
	A HORES	29 galactosi0ase							

GLP1R interactors and phenotypic factors sorted by Influence, Connectivity and Stability

Case Study: Lung Cancer

Innovate

UK

CATAPI

Project led by Intellomx

Grant. Subcontractors

Discovery Catapult and cell-line robotics company

included: Medicines

and supported by Innovate

ARCTORIS

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)



IO:03 KRAS inhibitor

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

IO:04 KRAS/MEKK inhibitor

10:0404 Small molecule **10:0405** Small molecule

IO:02 MEKK inhibitor

IO:0202 Small molecule wild

wild type+G12C

G12C

G12C

• 3 biological targets and 7 molecules prioritized for development and partnering

Case Study: IPF

- Question: are we able to identify causal factors/drivers of Idiopathic Pulmonary Fibrosis
- Publicly available transcriptomic data set analyzed GSE150910 103 IPF cases, 104 Non-IPF case
- Key pathway used as interrogation framework
 Pathway: Cellular Senescence 127 gene products
- Entire transcriptome analyzed for associations with selected pathway components
- Key features available for consideration in ranking:
 - Influence of a given gene product in the network
 - Influence of disease network on gene product
 - Degree of pathway connectivity
 - Stability of gene product across the population
 - Gene influence in healthy lung, liver and blood
- Work-in-progress ...

		Pathway					
Gene	In Cellular	Miner	Conn ectivity	Influence	Stability	OVERALL	
entifier	Senescence list	Conn ectivity	Rank	Rank IPF	Score	RANK	Protein Class
31	NO	20	114	49	44	1	apoptosis inhibitory protein
826	NO	18	190	32	81	2	metalloprotease
161	NO	21	76	158	85	3	oxidoreductase
139	NO	18	190	98	47	4	Golgi-localized complex
643	NO	21	76	177	99	5	Solute Carrier Protein
672	NO	17	228	116	12	6	C2H2 zinc finger transcription factor
666	NO	14	342	18	20	7	regulator of G protein signaling
376	NO	16	266	27	101	8	membrane traffic protein
293	NO	15	304	24	88	9	GTP-binding elongation factor
683	NO	18	190	131	102	10	RNA Binding Protein
279	NO	14	342	44	46	11	membrane traffic protein
601	NO	16	266	62	107	12	RING Finger Protein
599	NO	18	190	208	48	13	ubiquitin-protein ligase
470	NO	14	342	104	4	14	regulatory protein
201	NO	19	152	288	17	15	mannosyltransferase activator
4	NO	14	342	101	29	16	scaffold/adaptor protein
46	NO	20	114	341	23	17	transmembrane protein dislocase
412	NO	11	456	15	14	18	phosphatase
339	NO	11	456	26	5	19	scaffold/adaptor protein
734	NO	14	342	51	95	20	Kelch Like Family Member



Case Study: Breast Cancer

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• Question: can we identify markers that predict proliferation in breast cancer?





Datasets: Nottingham, Uppsala, Metabric and TCGA breast cancer tissue expression array data. (3554 cases). 34 genes found consistently in the top 100 PANN ranked genes out of 50,000 genes across 5 questions across 3 data sets

SPAG5 (Hub) validated as new driver of breast cancer

Case Study: TB Diagnostic Discovery



Intellomx receives coveted approval in China

The Ministry of Science & Technology (MOST) in Beijing announced this week that UK drug-discoven Al company Intelligent OMICS has been granted approval for its Tuberculosis study in Wuhan, China.

The study aims to validate both a panel of diagnostic biomarkers that predicts the presence of latent Fuberculosis and to validate potential biological drug targets that provide new treatment options.

Approval enables data to be shared for the first time between Wuhan Pulmonary Hospital and the company's research team. Transfer of genetic material and data is strictly controlled within China and has proved a significant challenge for western pharmaceutical and blotech companies. It has taken Intelligent OMICS two years to achieve this valuable milestone under China's Huma Genetic

> understanding of the underlying disease pathways. This is clearly valued in China - as well as in India and

her geographies with a high TB burden. Ultimately, we expect to apply this search to identify new therapies for TB that take effect prior to the

cquisition of drug resistance so that we can address the twin issues of latent B and multi-drug resistance infection. But first, we are absolutely delighted b e able to progress this important study in China and look forward to intellow. Wuhan

"Curtemin China, led by MN Nicole Song, hav worked trielessly to address the complexities of Chinase regulation," comments the Intellation Director Dr Simon Haworth. "Few International companies have achieved thit Approxil, making cross-bodie genetics-related research impossible for most. But TB is a critical global issue and our ability to diagnoce TB in its latent, hidden state is going to make a very similarat market in disease prevention and in

20 Dec 2023

Resources Administrative Licensing regulations

porting results in O2 2023."

"We believe this work will herald a new beginning for TB treatment and prevention." *"There is no gold standard test for LTBI (Latent TB Infection)."*





Updated and consolidated guidelines for programmatic management

Latent

berculosis

infection

WHO 2024

• **Question**: Can we create a diagnostic to differentiate between latent and active Tuberculosis?

Category	Test	Active TB	Latent TB ¹	BCG ²
Host response	TB-PRECISE	\checkmark	\checkmark	\checkmark
Host response	MTB-HR	 Image: A start of the start of	\mathbf{x}	\checkmark
Skin test	TST		\mathbf{x}	×
IGRA	QFT-Plus	 Image: A start of the start of	\otimes	×
Live bacteria	Actiphage		×	\checkmark

test provides sensitivity and specificity >85%
 test results unaffected by patient BCG status

Note: Generalisation

Markers refined in the Intellomx Han Chinese population trial were originally identified in Caucasian and South African datasets using alternative data collection methods. This provides a high degree of confidence in the applicability of TB-PRECISE in the wider global population.

Validation

Intelligent OMICS

Intellomx output has been validated in multiple disease areas and clinical contexts. Examples:

Lung cancer

-								
Control	10:0405	10:0404		Control	10:0301	10:0302	10:0303	
Table Same Table	100 100 100		Total ERM 1/2					Total ERK1/2
Them Name States			prisongetso- ERRES/Z					Vincutin
			Vinculin	The second				phospha-ERK10
Control IO:030	12 10:0303	10:0301						VICAN
		===	Total ERH(1/2		Control	10:0202		
and the loss have been	3004 000 000 000		vinculin phospho-ERK1/2				Total ERK1/2	
			Vinculin		No. 848.88	AL	phospho-ERI	(1/2
Contro	al 10:0202				1000 Boot Bo		Vinculin	
		Tutal ERHID						
100.00	-	phospho-Er	RH 1/2	117		C3 #6989		
		a Vancoura		124				- popla in
1.102	SURGERS &							
12-1	-					-		
				3.00				
				a		_		
22.1				10:0301	10:0302	10:0303	10:0202	
10:0405 10:0404	10:0302 10:0303 H	0.0301 10:0202						

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 results validated in Wild Type and Mutated cell lines

"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."



CEO



ARCTORIS

Breast cancer



SPAG5 (Hub) validated in >15000 cases -Chemotherapy response. Cell line studies show functionality. P(false discovery) <1x10⁻⁷⁸



SPAG5: new driver of proliferation validated in over 15,000 cases. Patent Ref: US10775381B2

Tuberculosis

TB diagnostic tested in the Han population, showing high sensitivity and specificity. Work ongoing for a multi-site clinical trial in China.

Trial results	Sensitivity	Specificity	AUC	Markers
Latent v Control	100%	87.9%	0.82	4
Active v Control	100%	100%	1.00	4
Active v Latent	100%	93.0%	0.91	5



Celebrating successful validation of our TB Diagnostic with the UK Dep Consul General in Wuhan, the the hospital Chairman and team

Plant biology



Two transcription factors were discovered using data mining and Network Inference. Development of transgenic fruit demonstrated on/off switching of ripening.





Intellomx I³ recap



I ³ -Distiller	Identification of key genes
I ³ -Driver	Identification of key disease drivers
I ³ -Miner	Defining the disease pathway
I ³ -Digital Twin	Anticipating tox liabilities
I ³ -Pilot	Identification of novel Small Molecules and Biologics
l ³ -Precise	Panel optimization for diagnostics

The Intellomx I³ technology platform delivers validated targets, linked to *in silico* drug candidates.

Our algorithms deploy 5 layers of validation across multiple datasets, addressing data issues and dramatically reducing the probability of false discovery whilst our digital twins build comparator pathway models for healthy state in tissue of interest and in off-target tissues.

Results fill knowledge gaps based on evidence (whole transcriptome), quantifying the influence of each molecule in a pathway, identifying levels of dysregulation of each molecule and linking drug candidates with targets, ranked on multiple criteria.

The Intellomx I³ technology swarm-based approach is not constrained by the availability of compute resource. Our swarms undertake multiple analyses, ranking results by concordance, with the option to drill into any single result or group of analyses to facilitate understanding and derive optimal drug targets.

Intellomx I³: Intuitive, Informed, Intelligence

Our Clients





Key papers + illustrations:



MEMBERSHIP DIRECTORY

DDI & dru

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CONTACT US Lancet oncology 🐉 frontiers trontiers 🐉 obn.org.uk, if y Supplementary data available on request Frontiers in oncology Frontiers in biology CONNECT 💃 🕕 SPAG5 as a prognostic biomarker and chemotherapy sensitivity predictor in breast cancer: a retrospective, integrated genomic, transcriptomic, and protein analysis Development of a Bioinformatics Tarek M A Abdel-Fatah*, Devika Aganwal, Dong-Xu Liu, Roslin Russell, Oscar M Rueda, Karen Liu, Bing Xu, Paul M Moseley, Andrew R Green, **Comprehending Meningioma** Framework for Identification and Alan & Packley, Robert C Rees, Carlos Caldos, Jan O Filis, Gcabam R Ball*, Stenben YT Char Signaling Cascades Using Validation of Genomic Biomarkers Plant physiology ances Jama network REGULAR ARTI **Blood** advances Driginal Investigation | Oncology Intelligent Network Inference Analysis Identifies an APRR2-Like Association of Sperm-Associated Antigen 5 and Treatment Response A parsimonic OMI CATAPLI Gene Linked to Pigment Accumulation in Tomato and in Patients With Estrogen Receptor-Positive Breast Cancer myeloid leukemia multicohort study Pepper Fruits^{1[W][OA]} Tarek M. A. Abdei-Fatah, HHD, Galam R. Ball, PHD, Palati U. Thangareku, PHD; Lymre E. Red, PHD, Amy E. McCart Reed, PHD; Jod M. Sauruz, PHD, Pascal H. G. Dagli, PHD; Peter S. Smipnon, PHD; Sauri R. Laham, MD; Lomire Kingge, PHD; Salida Gyöffly, PHD; Paul M. Moseley, BS; Urons), Andrew R. Geen, PHD, Alan G. Pockley, PHD; Confor Galada, Kim, Man D. BLK, Moselpeiner, T. Chan, DM Conquering KRAS! Sarah Wagner,¹ Jayakumar Vadakekolathu,¹ Sarah K. Tasian,² Heidi Altmann,³ Martin Bornhäuser,³ A. Graham Pockley,¹ Graham R. Ball,¹ Yu Pan, Glyn Bradley², Kevin Pyke, Graham Ball, Chungui Lu, Rupert Fray, Alexandra Marshall³, and Sergio Rutella¹ The AI drug discovery revolution that is here to stay Subhalai Jayasuta, Charles Baxter, Rik van Wijk, Laurie Boyden, Rebecca Cade, Natalie H. Chapman, Key Points John van Geest Cancer Research Centre, College of Science and Technology, Notingham Trent University, Notingham, United Kingdom; ⁹Division of Oncology and Center irr Childhood Cancer Research, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine; Philadelphia, PA; and ⁴Department of Internal Paul D. Fraser, Charlie Hodgman, and Graham B. Seymour* Question Are sperm-associated Intelligent OMICS is delighted to announce successful completion of its recent Innovate UK grant Division of Plant and Crop Sciences, University of Nottingham, Sutton Bonington, Loughborough LE12 5RD, IMPORTANCE There is no proven test that can guide the optimal treatment, either endocrine edicine I. University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany Detection of ham and Cop schedes, chivelengy of Normanna Satisfies Detection of Satisfies and Cop schedes, Chive Strangent, Scheder Scheder, Scheder Scheder Scheder, Scheder Scheder, Scheder Scheder, Scheder antigen 5 (SPAG5) transcript or protein program, in collaboration with the Medicines Discovery Catapult (MDC) and Arctoris Limited. erapy or chemotherapy, for estrogen receptor-positive breast cance expressions associated with treatment 5 key conclusions esponse in patients with estrogen kealott's Hill International Research Station, Bracknell, Berkshire RG42 6EY, United Kinedom (C.B.): Syncentic Acute myeloid leukemia (AML) is a genetically beterogeneous hematological malignancy Key Points OBJECTIVE To investigate the associations of sperm-associated antigen 5 (SPAG5) transcript and Biotechnology, Research Triangle Park, North Carolina 27709 (R.C.): and School of Biological Sciences, Royal receptor-positive breast cancer? with variable responses to chemotherapy. Although recurring cytogenetic abnormalities SPAGS protein expressions with treatment response in systemic therapy for estrogen recentor. · Application in oncology identifies novel KRAS-inhibiting drugs for lung cancer, one of which is Findings In this cohort study including even effective regardless of KRAS mutation Machine-learning a and gene mutations are important predictors of outcome, 50% to 70% of AMLs harbor normal positive breast cancer Holloway University of London, Egham Hill, Egham TW20 OEX, United Kingdom (P.D.F. proaches identified a 12720 patients with estrogen recepto or risk-indeterminate karyotypes. Therefore, identifying more effective biomarkers · Al-driven drug discovery is at last proven, and ready for application across multiple diseases parsimonious gene DESIGN, SETTINGS, AND PARTICIPANTS This retrospective cohort study included patients with e breast cancer. SPAGS transcri predictive of treatment success and failure is essential for informing tailored therapeutic · The AI approach discovers new drugs because it focusses on the drivers or causes of the disease expression signature estrogen recentor, positive breast cancer who received 5 years of adjuvant endocrine therapy with or and SPAG5 protein overexpressions decisions. We applied an artificial neural network (ANN)-based machine learning approach state, rather than focussing on the symptoms or effects of a disease state: Carotexistis papearst some of the most important secondary metabolites in the human dist, and tuman (Soliam Igoperation) is a first source of the source of Carotenoids represent some of the most important secondary metabolites in the human diet, and tomato (Solanum lucoversicum) is a that predicts risk in without neoadiuvant anthracycline-based combination chemotherapy (NACT) derived from 11 to a publicly available data set for a discovery cohort of 593 adults with nonpromyelocytic The evidence-based analysis produces original results, without reliance on prior hypotheses or newly diagnosed AML roborts from December 1 1986, to November 28, 2019. The associations of SPACS transcript and in patients who received endocrine literature, allowing creation and control of new Intellectual Property. ML. ANN analysis identified a parsimonious 3-gene expression signature comprising SPAGS protein expression with pathological complete response to NACT were evaluated, as was the therapy alone. Overexpressions of • The 3-gene PI could CALCRL, CD109, and LSP1, which was predictive of event-free survival (EFS) and overall · Al discovery methods can achieve greater than 90% reduction in carbon footprint compared to association of SPAGS mRNA expression with response to neoadjuvant endocrine therapy. The SPACS transcript or SPACS protein war be used to refine the survival (OS). We computed a prognostic index (PI) using normalized gene-expression level traditional high-throughput screening associations of distal relapse-free survival with SPAG5 transcript or SPAG5 protein expressions were accuracy of patient and B-values from subsequently created Cox proportional bazards models, coupled with therapy but sensitivity to analyzed. Data were analyzed from September 9, 2015, to November 28, 2019 The project, led by Intelligent OMICS and funded by Innovate UK, sought to demonstrate the carbon stratification and clinically established prognosticators. Our 3-gene PI separated the adult patients in each anthracycline-based combinatio outcome prediction in efficiency of an AI-based drug discovery program compared to traditional pharma methods. The case European LeukemiaNet cytogenetic risk category into subgroups with different survival MAIN OUTCOMES AND MEASURES The primary outcomes were breast cancer-specific surviva therapy, and downregulation o outine clinical practice study used in the project was assessment of Non-Small Cell Lung Cancer - thought to account for probabilities and identified patients with very high-risk features, such as those with a high pepper (Capsicum annuam) 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. distal relapse-free survival, pathological complete response, and clinical response. Outcomes were SPAG5 during the course of preoperativ over 80% of all lung cancer cases examined using Kaplan-Meier, multivariable logistic, and Cox regression models systemic therapies was associated wit PI and either FLT3 internal tandem duplication or nonmutated nucleophosmin 1. The PI clinical benefit. remained significantly associated with poor EFS and OS after adjusting for established RESULTS This study included 12 720 women aged 24 to 78 years (mean [SD] age, 58.46 [12.45] prognosticators, and its ability to stratify survival was validated in 3 independent adult Tomato (Solanum lucopersicum) is a climacteric fruit for studying ripening in fleshy fruits because of the Meaning These findings suggest that The team analysed nine lung cancer datasets from the Intellomx Curated Data Library, using the years) with estrogen receptor-positive breast cancer, including 1073 women with SPAGS transcript cohorts (n = 905 subjects) and 1 cohort of childhood AML (n = 145 subjects). Further in silico where ripening is initiated and coordinated by ethylene exceptional genetic and molecular resources that are SPAGS transcript or SPAGS protein Intelligent OMICS Is platform. The datasets include human transcriptomic data plus confirmation of a ecceptional generic and molecular resources into are available, induding well-characterized mapping popu-lations (Lippman et al., 2007), numerous single-gene mutants, noutine transformation, and a fully annotated genome sequence (Tomato Genome Consortium, 2012). expression and 361 women with SPAG5 protein expression of locally advanced disease stage IIA (Alexander and Grierson, 2002). It is the model system analyses established that AML was the only tumor type among 39 distinct malignancies for expression could be used as a clinical ough IIIC. Women with SPAG5 transcript and SPAG5 protein expressions achieved higher disease v healthy diagnosis for lung cancer for approximately 2,000 patients. Proprietary AI was used tool for selecting and monitoring which the concomitant upregulation of CALCRL, CD109, and LSP1 predicted survival. to model the underlying systems biology - first creating a list of the most important genes defining pathological complete response compared with those without SPAGS transcript or SPAGS protein 1 This work was supported by the Biotechnology and Biologica response to neoadjuvant therapies and Therefore, our ANN-derived 3-gene signature refines the accuracy of patient stratification rript: odds ratio, 2.45 [95% CI, 1.71-3.51]; P < .001; protein: odds ratio, 7.32 [95% the disease v healthy diagnosis, then modelling the interaction of those genes in a disease pathway Sciences Research Council ESB-LINK program (grant nos. BB/ R005458 to T.C.H. and G.B.S. and BB/F005350/1 to P.D.F.), the ERAguide adjuvant therapy in estroger The repertoire of well-characterized mutations in tomate and the potential to significantly improve outcome prediction. CI, 3.33-16.22]; P < .001). Adding adjuvant anthracycline chemotherapy to adjuvant endocrine map based on the evidence in the data. has permitted the identification of genes that encode receptor-positive breast cancer NET TomQML program (grant nos. BB/GO2491X to G.B.S. and BB) has permitted the identification of genes that encode proteins that govern the ripering process. These have included Never-ripe (Nr), ripering-inhibitor (rin), non-ripering (nor), and Colorless nonripering (Cm). Mutations at these loci can completely abolish normal ripering therapy for SPAGS mRNA expression in estrogen receptor-positive breast cancer was associated with Introduction 6024901/1 to P.D.F.), and the TomNet project (grant nos. BB/J01607/ 1 to P.D.F. and BB/J015598/1 to G.B.S.). All awards were in collab-"The real benefit of our technology is evident when we compare our results with what is known in prolonged 5-year distal relapse-free survival in patients without lymph node involvement (hazard atio, 0.34 [95% CI, 0.14-0.87]; P = .03) and patients with lymph node involvement (hazard ratio, + Supplemental content the literature," says Intellomx CEO Dr Simon Haworth. "We can immediately spot errors and ation with Syngenta Seeds omissions in pathway maps documented in KEGG, for example, and because our analysis only Acute myeloid leukemia (AML) is characterized by bone marrow (BM) and tissue infiltration by ² Present address: GSK Medicines Research Centre, Gunnels 0.35 [95% Cl. 0.18-0.68]: P = .002) compared with receiving 5-year endocrine therapy alone. Mean Author affiliations and article infor Wood Road, Stevenage, Hertshire SG1 2NY, UK (Lanahan et al., 1994; Vrebalov et al., 2002; Mannin et al., 2006). The NR, RIN, CNR, and NOR gene prod (SD) SPAG5 transcript was found to be downregulated after 2 weeks of neoadjuvant endocrin focusses on the most influential drivers in each pathway we know that any such differences are 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 ³ Present address: Ashworth Laboratories, King's Buildings, Uni-ersity of Edinburgh, Edinburgh EH9 3JT, UK. genuinely important. For our lung cancer work, focussing on EGFR and KRAS, the comparison led therapy compared with pretreatment levels in 68 of 92 patients (74%) (0.23 [0.18] vs 0.34 [0.24] ucts, along with those from tomato HD-Zin be cured in 35% to 40% of adult patients aged < 60 years with multiagent chemotherapy and often hematopoietic stem cell transplantation (HSCT), chemorefractory disease is common, and relapse protein1 (LeHB1), Tomato AGAMOUS-LIKE1 (TAGL1) APETALA2 (AP2; Lin et al., 2008; Itkin et al., 2009 P < .001) us to 8 really exciting new lung cancer targets. Corresponding author; e-mail gmham.seymour@nottingham.ac offailure,^a Investig w molecularly targeted agents fo the author responsible for distribution of materials integral to the The next step of the process was to validate in silico targets in the wet lab, to link validated targets children and adults with high-risk AML remains a high priority.^{4,5} Vrebalov et al., 2009; Chung et al., 2010; Karlova et al. findings presented in this article in accordance with the policy de-scribed in the Instructions for Authors (www.plantphysiol.org) is: to possible drugs and then to test the impact of those novel drugs on cancer cells. 2011), and others govern the onset and progression o 2011) and others govern the other and propression or the ripering Despite a growing understanding of this high-level regulatory network, the links to hormonal cues, plastic signals, and downstream effectors mediat-ing alterations in color, texture, and flavor are still poorly interval. ham B. Seymour (graham.seymour@nottingham.ac.uk) Subcontractor Arctoris, with its world leading fully automated drug discovery platform and roboti The online version of this article contains Web-only data. Open Access articles can be viewed online without a subscrip abmitted 31 December 2018; accepted 13 March 2019. DOI 10.1182/ © 2019 by The American Society of Hernatology 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 by full-text version of this article contains a data supplement Comment Access. This is an open access activity distributed under the terms of the CC-RV License www.plantphysiol.org/cgi/doi/10.1104/pp.112.212654 understood. ork Open. 2020.3(7) e209486. doi:10.1001/lamanetworkopen.2020.9486 July 7.2020 1/3 Plant Physiology®, March 2013, Vol. 1 113, Vol. 161, pp. 1476-1485, www.plartphysiol.org © 2013 American Society of P1 Downloaded from on April 3, 2020 - Published by www.plantphysiol.org Copyright @ 2013 American Society of Plant Biologists. All rights reserved. of Plant Biologists. All Rights Reserv 23 APRIL 2019 - VOLUME 3, NUMBER 8 Press service om: https://iamanetwork.com/ on 07/07/2026

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Differentiation vs Large Language Models and other Al approaches



Traditional Pharma Model



Slow and expensive Lab-based Constrained by hypotheses

1st Generation Al



Based on LLMs, Deep Learning or Binary Classifiers High computational requirement - inefficient Prone to false discovery and interpretation. Difficult to explain Over-reliant on known biology

2nd Generation AI



Swarm-Based Neural Networks – Optimised parallel computing Extensive cross-validation through concordance Explainable – Knowledge Graph easily interpretable Evidence-based on mathematics, not language Reveals the hidden biology of disease Multi-parameter probability ranking – optimised drug targets

Differentiation vs Large Language Models and other Al approaches



	Benefit		InSilico	Exscientia	Owkin	In Sitro	Precision
Evidence based, data driven approach to biomarker discovery	 Avoids bias of LLMs Reveals novel biology Eliminates false discovery 		×	×	\checkmark		
Network Inference modelling determines molecular causality	 Quantifies pathway Reveals drivers Determines dysregulation Facilitates digital twin 		×	×	×	×	×
Reliant on human disease tissue	 Clinically relevant Eliminates bias/downstream failure of cell/animal models 	\checkmark	×	×	\checkmark	×	
Target biomarker discovery matrix	 Systematically evaluates whole transcriptome Rapidly determines actionable targets (10 parameters) 		×	×	X	X	×

Differentiation vs Large Language Models and other Al approaches



Discovered and in the literature -Discoverable by LLMs from the literature -

de novo discoveries from Molecular data

We DON'T rely on flawed reductionist knowledge graphs or literature mining to identify the key drivers of each disease.

Instead, we use de novo, evidencebased modelling that discovers the underlying systems biology of each disease by direct analysis and then exploits that knowledge to create a stream of new drugs.

What happens next?



From first contact to project initiation typically takes 6 weeks. At first meeting the Intellomx team explains the utility and validation of the I³ tool box, reveals prior work in the disease area of interest and reviews what progress has already been made by the partner company. The team then helps clarify the clinical questions that need to be answered (see common queries at each research stage below).

Following the meeting, the Intellomx team reviews possible data sources and provides a formal proposal for review.

Disease Pathway Target Drug Trials

 \bigcirc

At the disease level, can we develop a new Diagnostic? Discern disease progression – systems biology v clinical standard? Factors controlling exacerbation?

Which are the most important targets, ranked?Can we identify the underlying disease pathway from scratch?Do the known pathways omit critical biology?What are the causal factors driving the pathway?Personalised meds: is the pathway consistent for all patients?

Have we selected the right target?

Rank targets according to 7 criteria (eg tox, druggability, stability) How does target A compare to target B in terms of tox elsewhere? Is there a better target than the one held by our competitor?

Companion diagnostic? Complementary target/drug? For investors: does the asset holder understand the underlying systems biology? Data Proposal

Contact



"To complete a long journey, it really helps if one sets off in the right direction. In our sector that basically means **selecting the right target**.

Our AI reveals the underlying biology of disease in order to identify optimum drug targets. *In silico* docking identifies drug candidates, and engagement with the full power of downstream AI enables us to de-risk drug development.

This is the decade in which the IP for a stream of new drugs will be secured, reversing the troubling trend in drug discovery globally. **Our technologies write the papers that LLMs will eventually read**."

Professor Graham Ball, Founder, Intellomx

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drug discovery Al

Case study: Schizophrenia





STEP 4

Maps novel targets for discove molecules linked to existing non-cancer drugs (reprofile) Molecules linked to existing cancer drugs



Network Inference identifies potential switch ending latency.

Primary analysis identified a small number of critical hubs that drive disease state, representing drug targets. NCEs and drugs for reprofiling have been identified that are linked to these targets.

Appendix II

Case study: COPD

STEP 3

MOLOGIC

STEP 2

Intellomx Distille

Intellomx Miner

STEP 4

cancer drugs

Intellomx Driver

Maps novel targets for discovery molecules linked to existing

non-cancer drugs (reprofile)

Molecules linked to existing



Refined panel:

12 features of 5 biomarkers



Intellomx POSitive service:

Mologic's COPD panel was highly effective but impractical to use due to high numbers of biomarkers. The Intellomx POSitive service enabled the panel to be reduced to 12 biomarkers.

Question: can we improve the Mologic

COPD panel for application on hand-held

Intellomx built a decision support model and code enabling the customer to deploy the companion diagnostic on mobile phone apps. biomarkers

Conclusion: Existing panel optimised and software provided for application on hand-held devices/mobile phone application

biomarkers

500

panel:

Original

Appendix II

Case study: Auto-immune Disease





STEP 4 Intellomx Driver

 molecules linked to existing non-cancer drugs (reprofile)
 Molecules linked to existing cancer drugs



Question: Can we develop new drugs for autoimmune disease?

Intellomx completed Primary Analysis for Autoimmune disease based on both client data and publicly available data, identifying 156 key genes mapped in the disease pathway.

The pharma co provided details of two targets: Target 1 was validated and linked to the disease pathway Target 2 was shown to be of negligible relevance in the disease





Analysis of a complex system to explain phenotype and stratification

Appendix II