Data Driven Precision Oncology

UNIVERSITY OF LIMERICK
OLLSCOIL LUIMNIGH

Limerick Digital Cancer Research Centre

Prof Aedin Culhane,
Limerick Digital Cancer Research Centre

@AedinCulhane Aedin.Culhane@ul.ie

Bioconductor
OPEN SOURCE SOFTWARE FOR BIOINFORMATICS

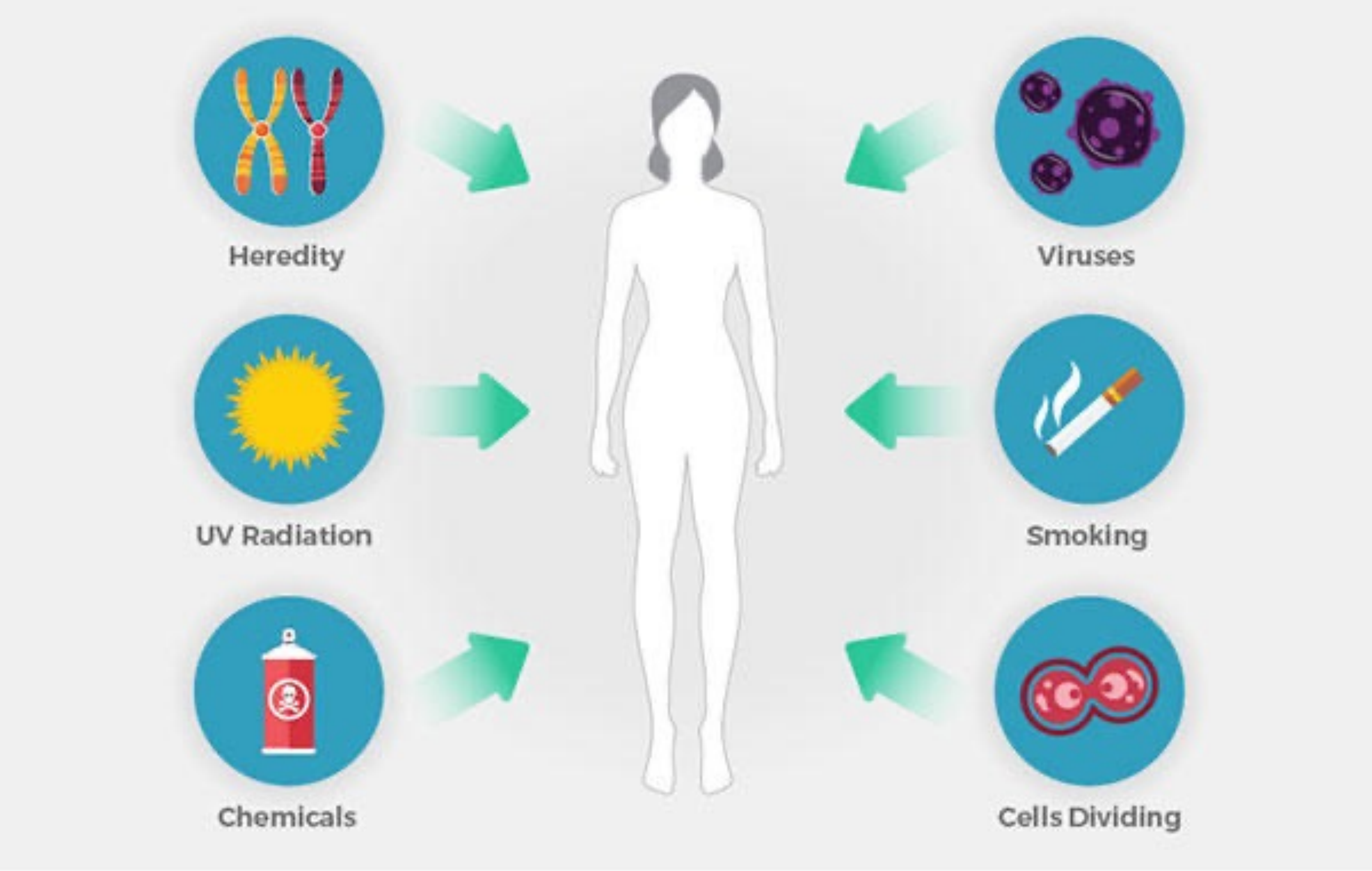
Overview of talk

- Briefly introduce computational oncology and our lab
- eHealth -Hub for Cancer
- Recent work
  - CAR T-Cell in renal cancer. Wang et al., Mol Ther Oncolytics 2021
  - Sensitivity to NK cell killing. Scheffer et al., Nat Genet. 2021
  - GVHD and tissue resident cells (unpublished)

Understanding cancer integrates data

- Genetic changes
- cause or increase the
- risk of cancer

- 1 in 2 people affected



Complexity of cancer : molecular basis of multicellular disease

- Human disease occurs within a complex milieu of cells
- Multiple body systems are involved in disease response;

  immune, lymph, nervous, endocrine
- Disease response involves local and systemic signalling and local tissue effects
- Harnessing the immune system

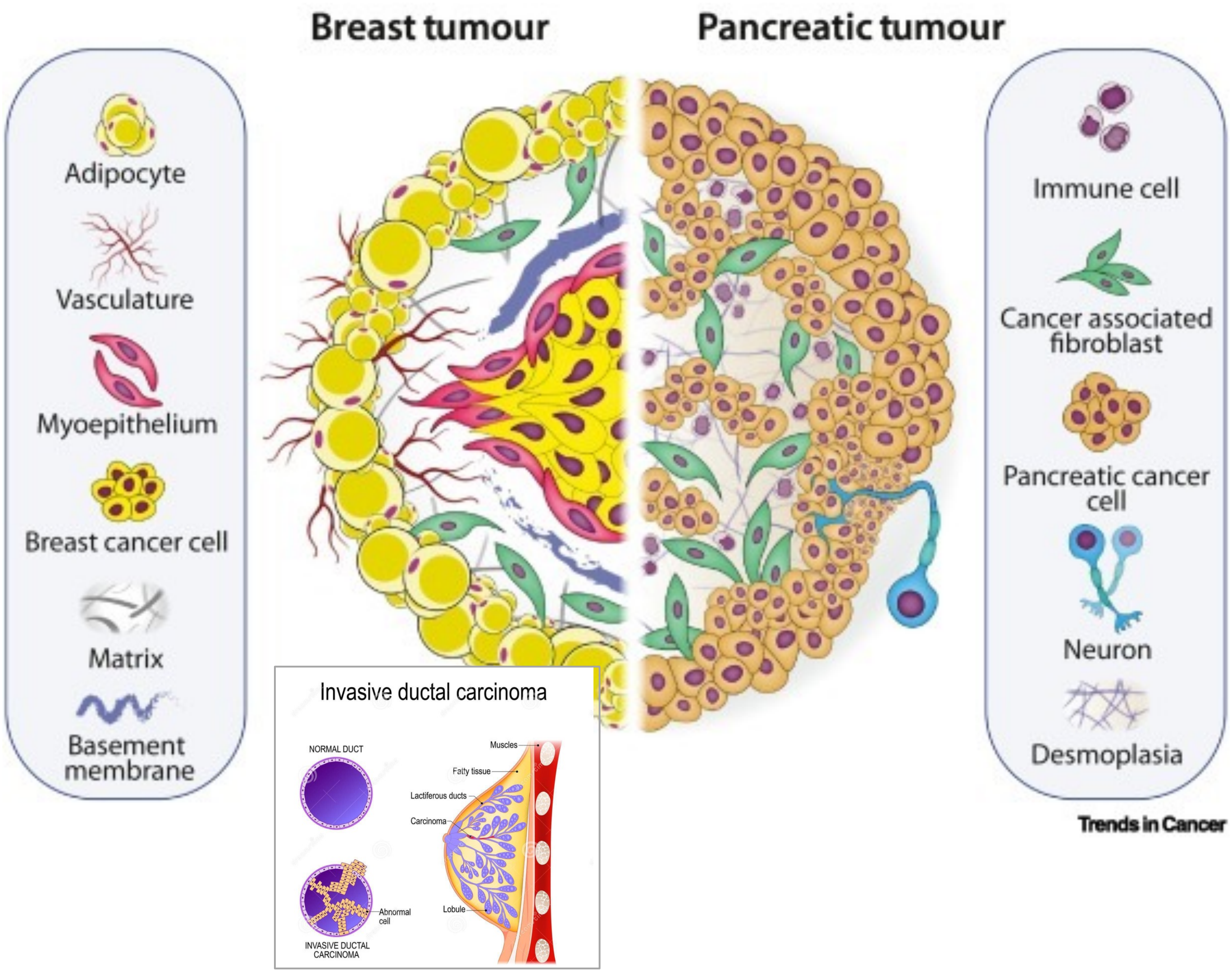
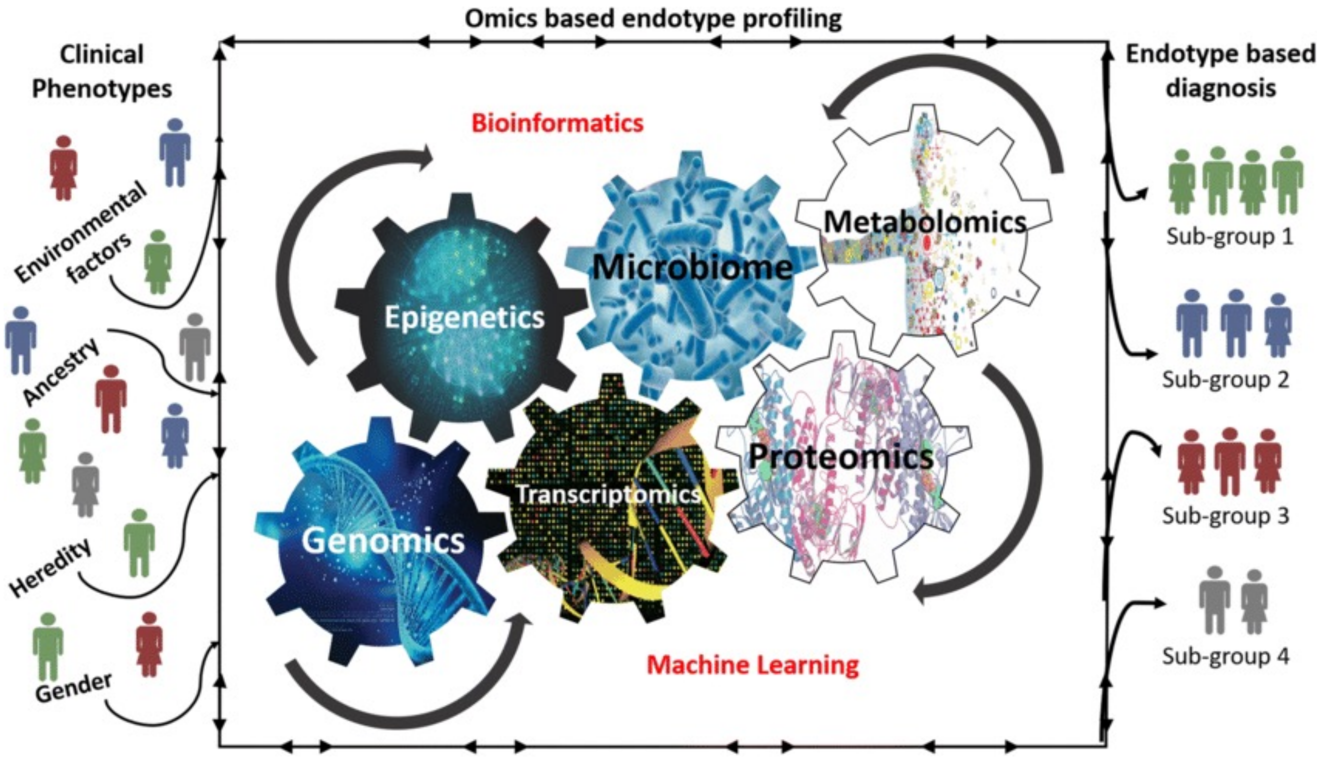


Figure from Carter et al., 2021, Trends in Cancer 7:11

Computational Oncology

- Transcriptomics
- Germline and somatic DNA changes
- Epigenetics
- Microbiome
- Metabolomics
- Integration with EHR
- Longitudinal, case/control, preclinical or phase I trial
- Multi’ omics integration



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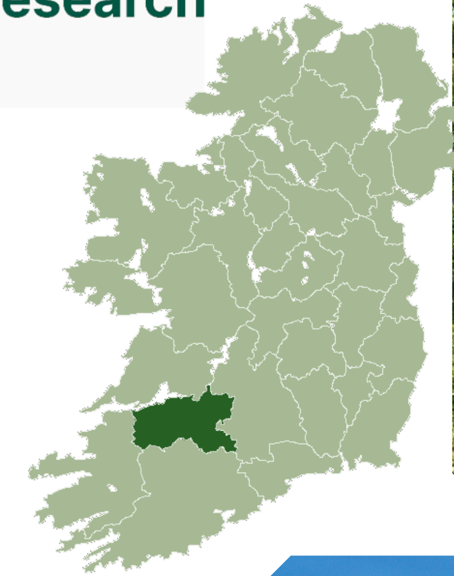
Limerick Digital Cancer Research Centre



Drawing on the collective expertise and resources of partners who have seen recent research investments totalling more than €300 million to develop digital personalised medicine to transform Cancer Care.

SFI Centre for Research Training in Foundations of Data Science

LERO Software for a better world

HRI health research institute

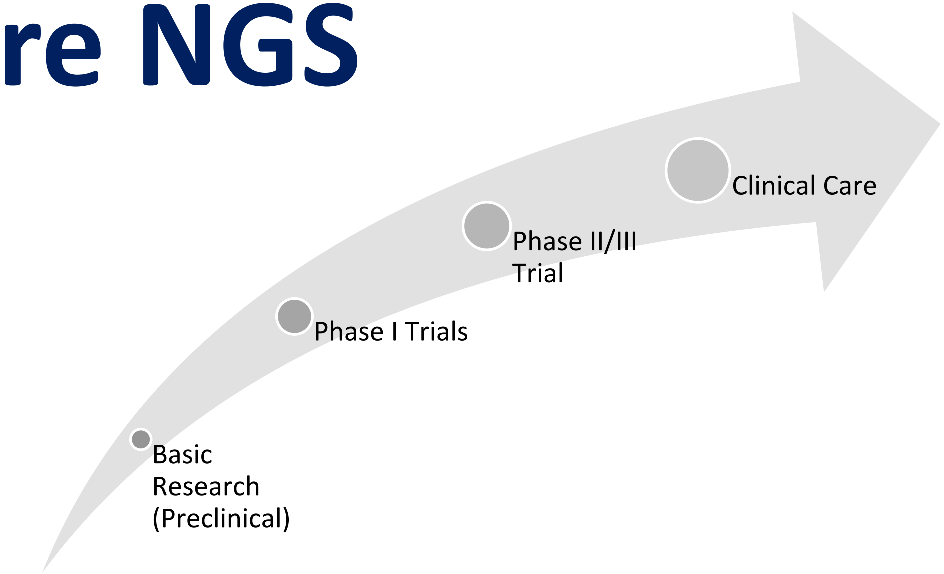
Bernal Institute

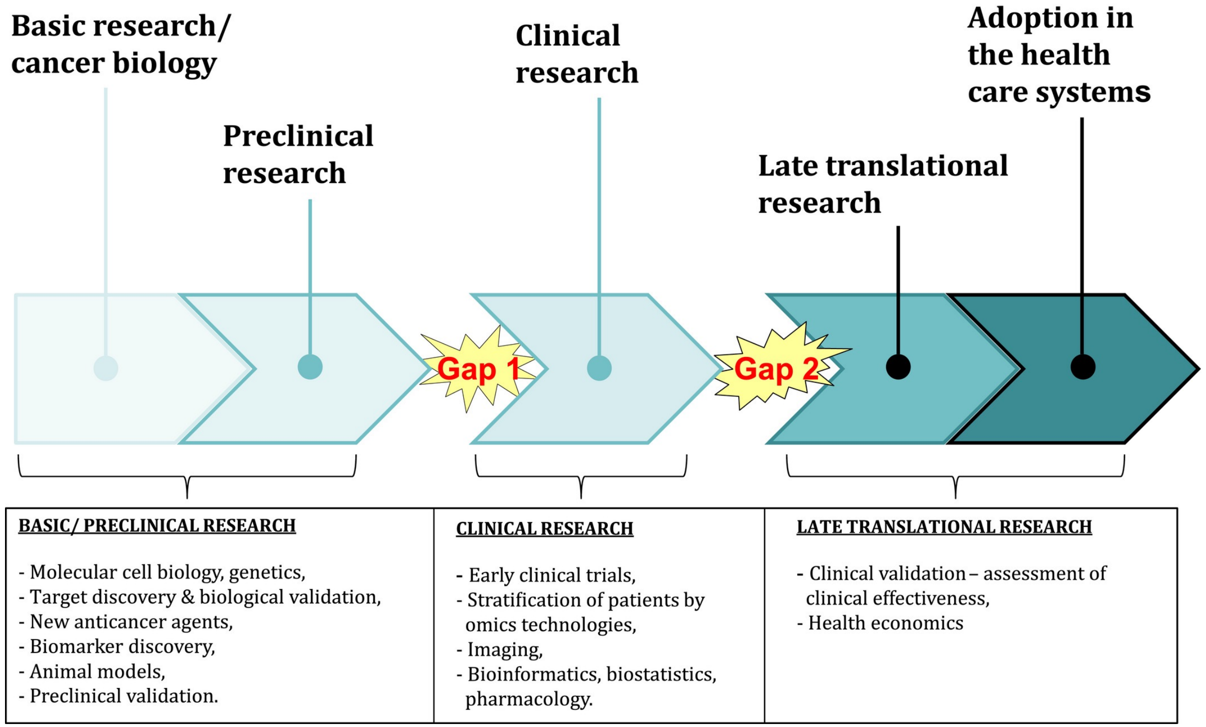
SSPC
SYNTHESIS AND SOLID STATE PHARMACEUTICAL CENTRE
Innovation Through Collaboration

Confirm Smart Manufacturing

Phase 0/1 clinical trial pipeline

Pre NGS

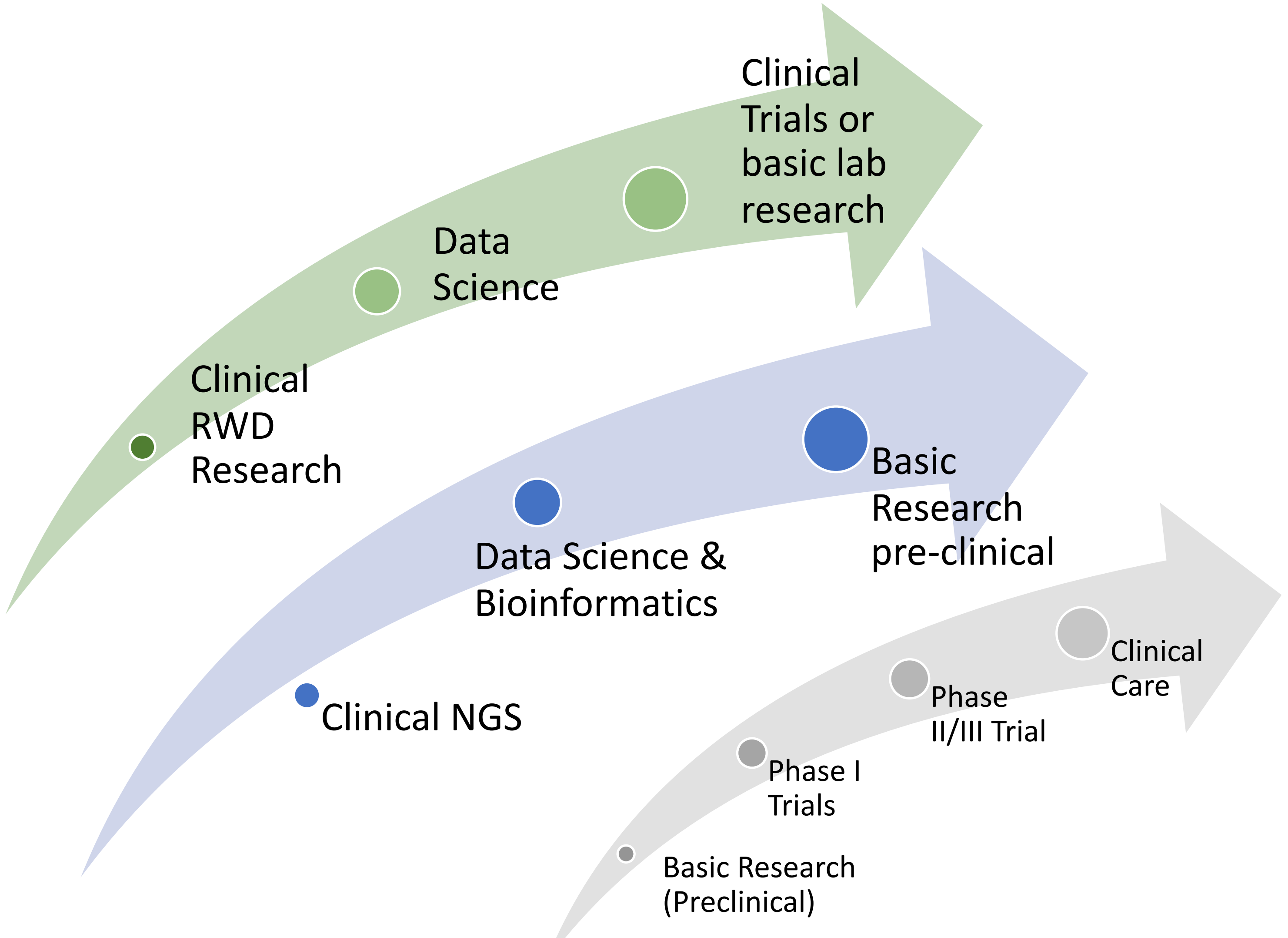




BASIC/ PRECLINICAL RESEARCH	CLINICAL RESEARCH	LATE TRANSLATIONAL RESEARCH
- Molecular cell biology, genetics, - Target discovery & biological validation, - New anticancer agents, - Biomarker discovery, - Animal models, - Preclinical validation.	- Early clinical trials, - Stratification of patients by omics technologies, - Imaging, - Bioinformatics, biostatistics, pharmacology.	- Clinical validation – assessment of clinical effectiveness, - Health economics

Celis, J.E. and Pavalkis, D. (2017), A mission-oriented approach to cancer in Europe: a joint mission/vision 2030. Mol Oncol, 11: 1661-1672. https://doi.org/10.1002/1878-0261.12143

Data Rich in Clinical Oncology Research



Clinical RWD Research

Data Science

Clinical Trials or basic lab research

Clinical NGS

Data Science & Bioinformatics

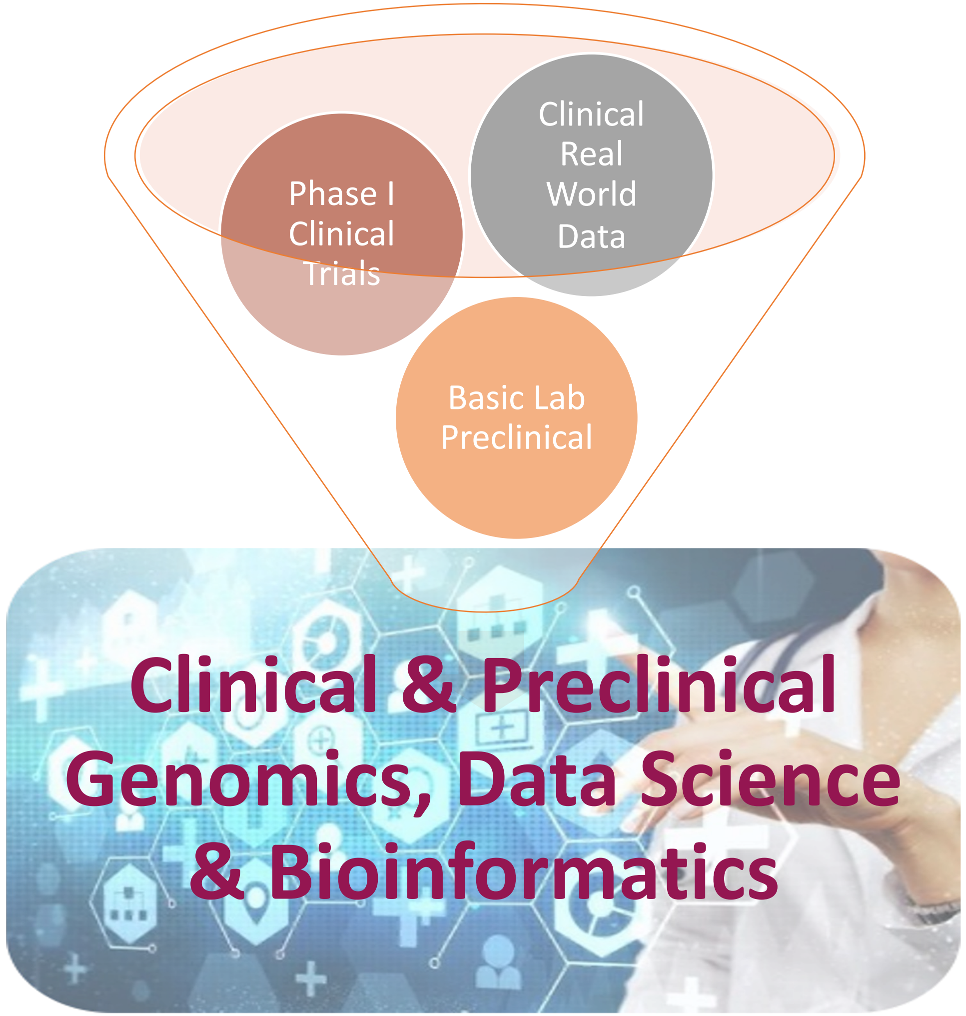
Basic Research pre-clinical

Basic Research (Preclinical)

Phase I Trials

Phase II/III Trial

Clinical Care



Phase I Clinical Trials

Clinical Real World Data

Basic Lab Preclinical

Clinical & Preclinical Genomics, Data Science & Bioinformatics

Recruitment to Clinical Trials in Ireland

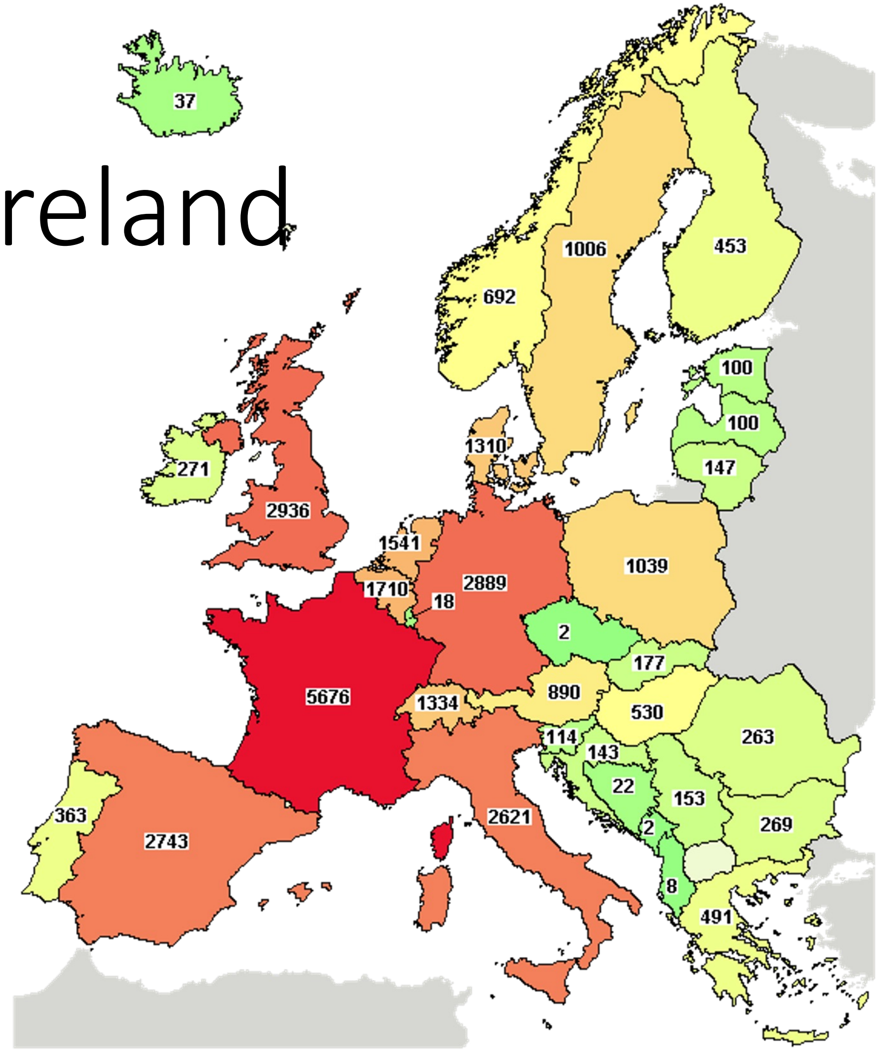
Patients have been shown to have significantly better outcomes by taking part in clinical trials.

Clinical trials enhance the value proposition for innovation and help us to attract global investments

But 2/3 Irish patients not offered CCT (Kearns et al., 2020). Lack access to structured routine care **clinicogenomic** data that can predict trial outcomes (Singal et al., 2019)

Lack of digital health data impediment to CCT

www.ipha.ie, Nov 11, 2020



https://clinicaltrials.gov/

Skills for Interoperable, Real-time, Real-World Data

eHealthHub


Rialtas na hÉireann
Government of Ireland

North South Research Programme
awards announcement

Strand II All-Island programme in federated eHealth cancer research awarded €4 million from the Shared Island Unit

eHealthHub

Mark Lawler (QUB)

Aedin Culhane (UL)

QUEEN'S UNIVERSITY BELFAST

DATA-CAN
The Health Data Research Hub for Cancer

Blood Cancer Network Ireland

N. IRELAND Cancer Registry

NUI Galway
OÉ Gaillimh

Saolta
Grúpa Ollscoile Cúram Sláinte
University Health Care Group

UCD DUBLIN

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

ST JAMES'S HOSPITAL

RCSI

BEAUMONT HOSPITAL

UNIVERSITY OF LIMERICK
OLLSCOIL LUIMNIGH

Ospidéil OL
UL Hospitals

National Cancer Registry Ireland

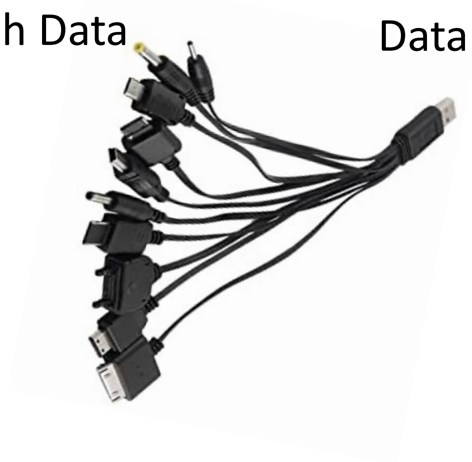
A SHARED ISLAND
THE FUTURE OF IRELAND

UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

CUH
Ospidéal Ollscoile Chorcaí
Cork University Hospital

North South Research Programme awards announcement

Heterogeneous Irish Data



Common Data Standard

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

- 4 Million Euro
- 10 PhD Students
- 4 Post doctoral Fellow
- 7 Research Assistants

eHealthHub

Interoperability, Standards

OHDSI Collaborators

Map of Collaborators

The OHDSI community brings together volunteers from around the world to establish open community data standards, develop open-source software, conduct methodological research, and apply scientific best practices to both answer public health questions and generate reliable clinical evidence.

OHDSI Collaborators

Our community is ALWAYS seeking new collaborators. Do you want to focus on data standards or methodological research? Are you passionate about open-source development or clinical applications? Do you have data that you want to be part of global network studies? Do you want to be part of a global community that truly values the benefits of open science? Add a dot to the map below and JOIN THE JOURNEY!

OHDSI By The Numbers

- 2,367 collaborators
- 74 countries
- 21 time zones
- 6 continents
- 1 community

OHDSI.org 10 #JoinTheJourney #JoinTheJourney 11 OHDSI.org

>800 Million EHR mapped to a standard format

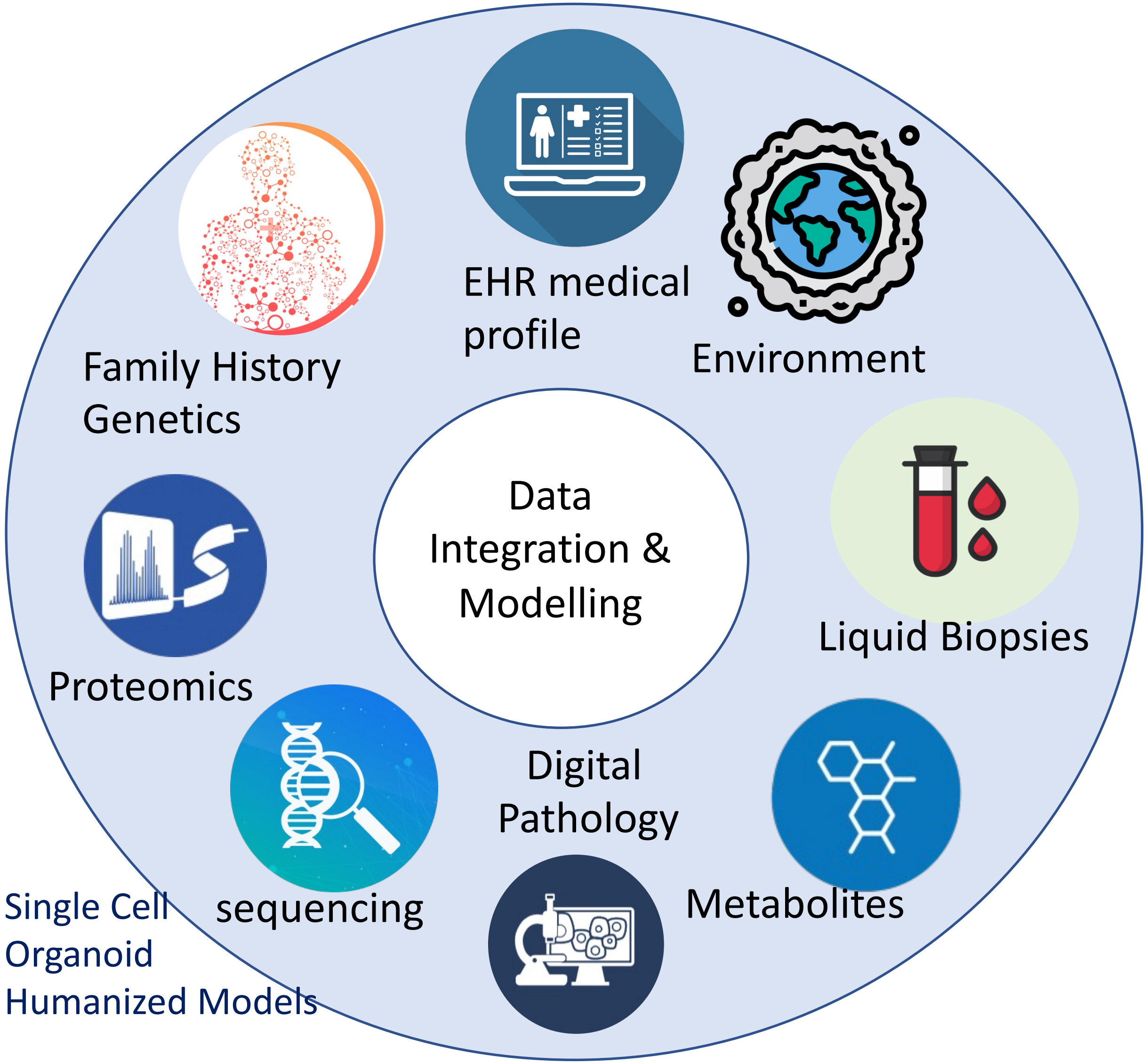
OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

HL7® FHIR®

Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM)

Health Level 7 International Version 2
Fast Healthcare Interoperability Resources

Digital Data in Cancer EHR



Family History
Genetics

EHR medical
profile

Environment

Data
Integration &
Modelling

Liquid Biopsies

Proteomics

Digital
Pathology

sequencing

Metabolites

Single Cell
Organoid
Humanized Models

Patient history
Co-morbidity

Drugs, treatments history

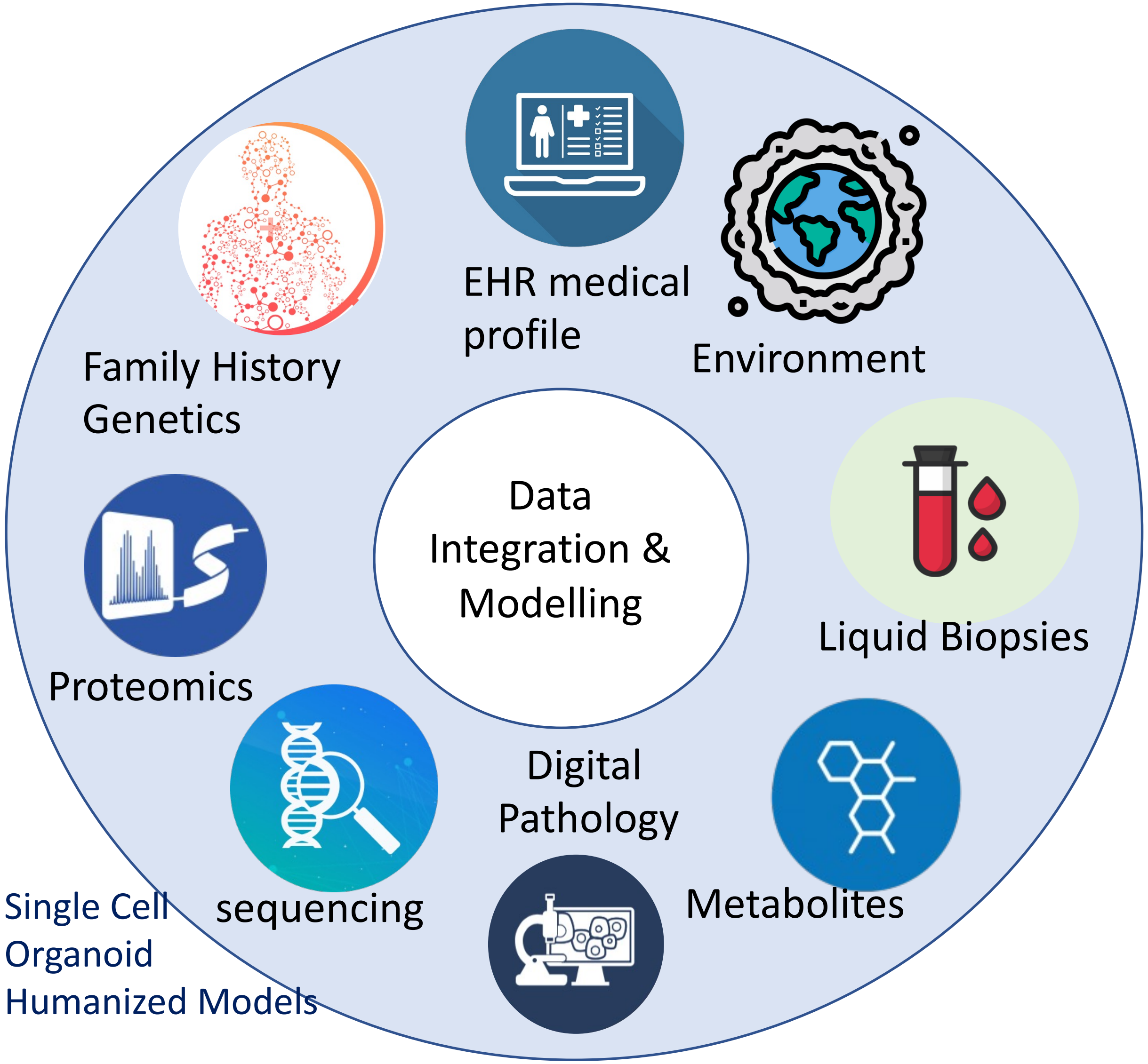
Pathology
Digital Pathology

Germline Genetics, family risk

Genomics
Blood tests (liquid biopsies)
Immuno-oncology

Mobile Apps -eg boutros bear

Cancer Digital Health



Family History
Genetics

EHR medical
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Single Cell
Organoid
Humanized Models

Data Science

Bioconductor
OPEN SOURCE SOFTWARE FOR BIOINFORMATICS

R

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

elixir

AnVIL

Technology

Federated
learning

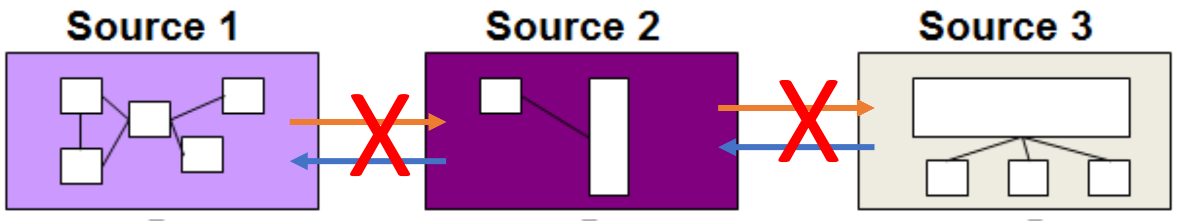
Cloud
computing

AI/ML

Connected
devices

What's so important about standards

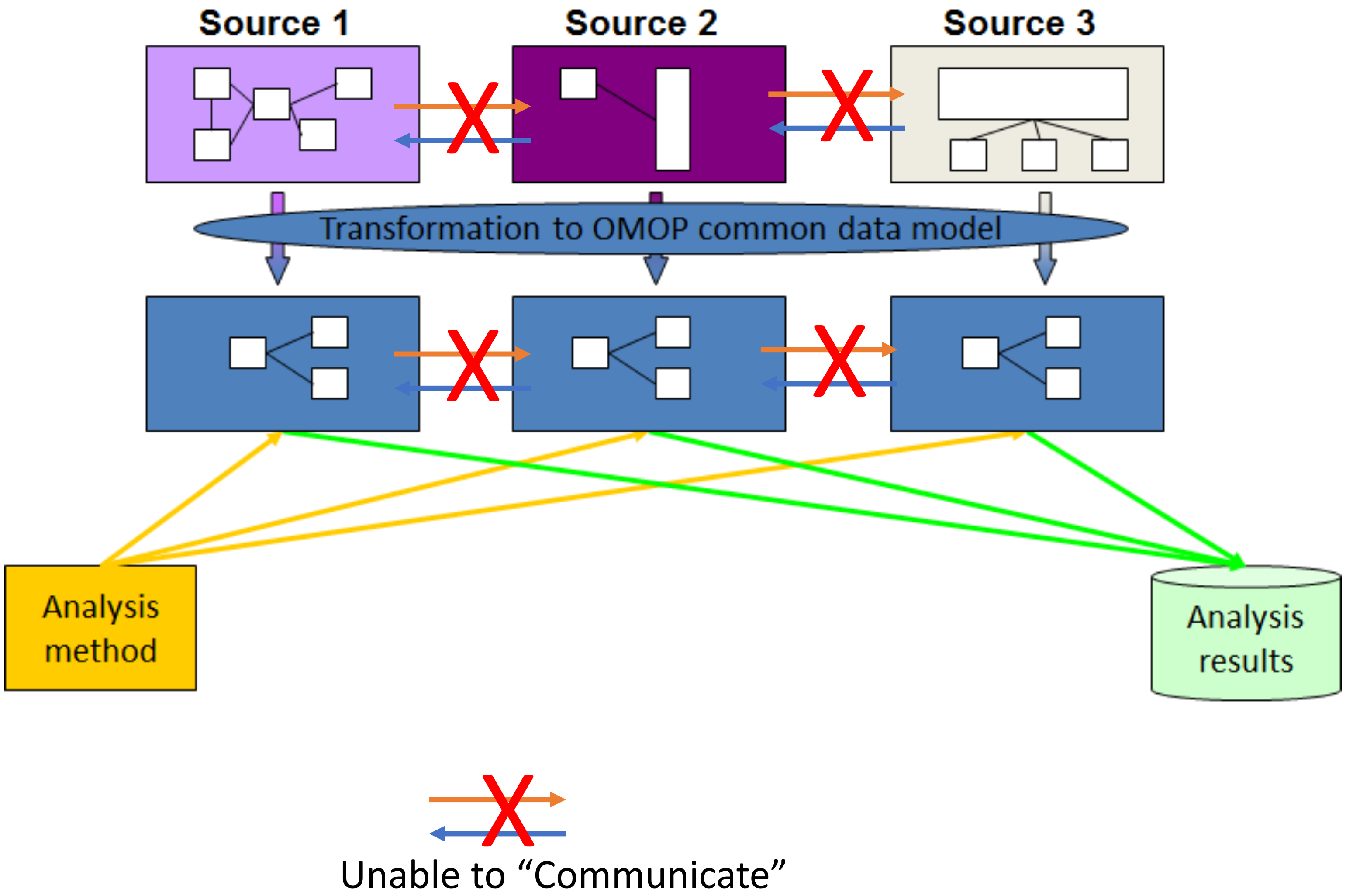
- Data source (EHR) is held locally within each site
- Researchers can query internal database
- Limited silos of data is a problem.
- Studies are underpowered especially in rare disease



Unable to “Communicate”

What's so important about standards

- Data can be locally secure
- but globally accessed
- Query can be sent to each data source
- Summarized results (not data) returned
- Aggregated over many



Real-time, Real-World Data

Findable
Accessible
Interoperable
Reusable

ABORATORS

OHDSI COLLABORATORS

p of Collaborators

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mmunity data standards, develop open-source software,
gical research, and apply scientific best practices to
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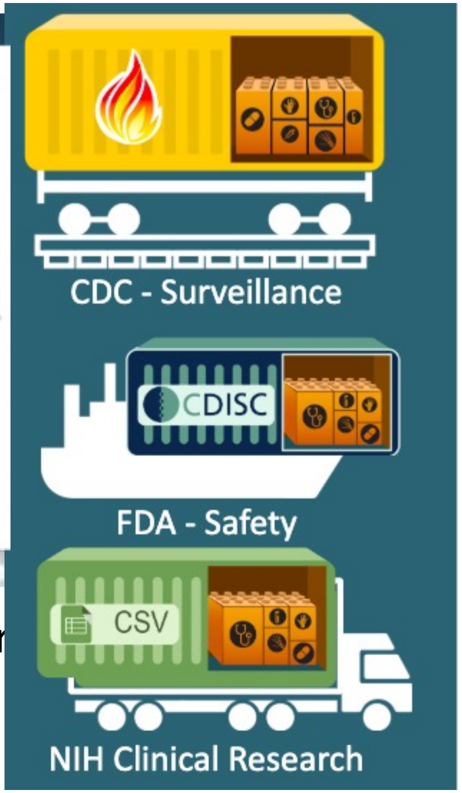
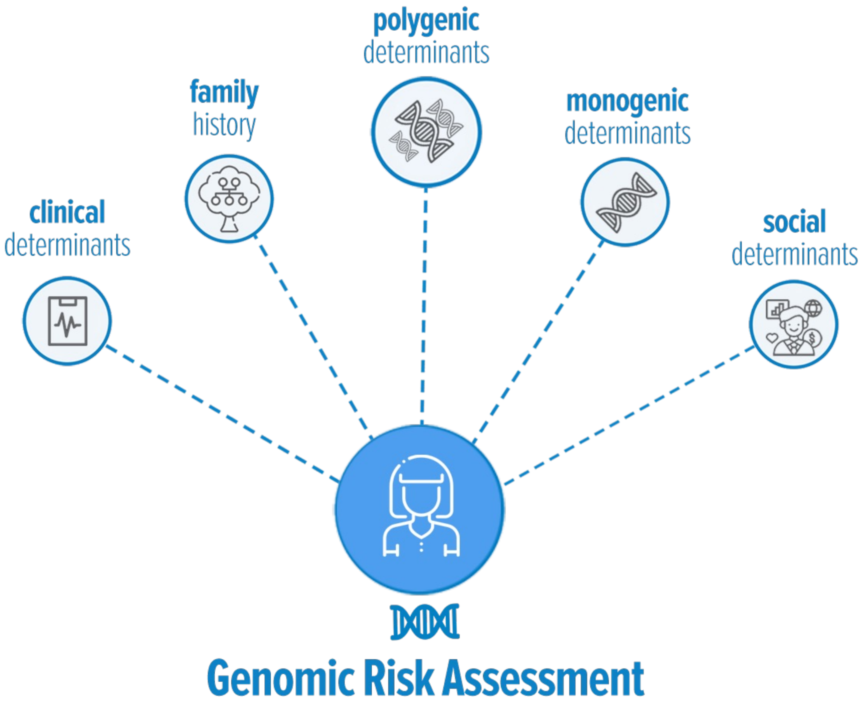


EHR Insurance & medical recor
inpatients, outpatient and GP
data mapped to a common
format provide
Real-time, real-world
surveillance and research

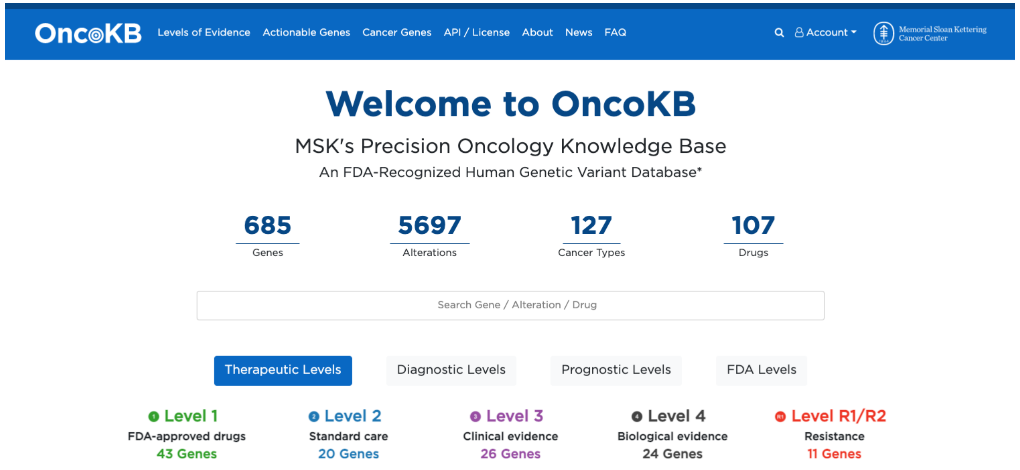
Observational Health Data Sciences and Informatics (OHDSI, pronounced "Odyssey") strives to promote better health decisions and care through globally standardized health data, continuously developing large-scale analytics and a spirit of collaboration though open science.

Founded in 2014, OHDSI is a growing collaborative of more than 2,300 researchers across disciplines (including biomedical informatics, epidemiology, statistics, computer science, health policy, clinical sciences), across stakeholders (including academia, industry, government and regulatory authorities, and health providers), and across geographies (including 76 countries and six continents). OHDSI also has established an international distributed data network that applies one open community data standard and collectively contains data for more than 800 million patients around the world, and has produce a suite of open-source software packages that enables the community to translate that data into reliable evidence.

Clinically actionable genes in EHR



*e*merge network
ELECTRONIC MEDICAL RECORDS AND GENOMICS



Welcome to OncoKB

MSK's Precision Oncology Knowledge Base

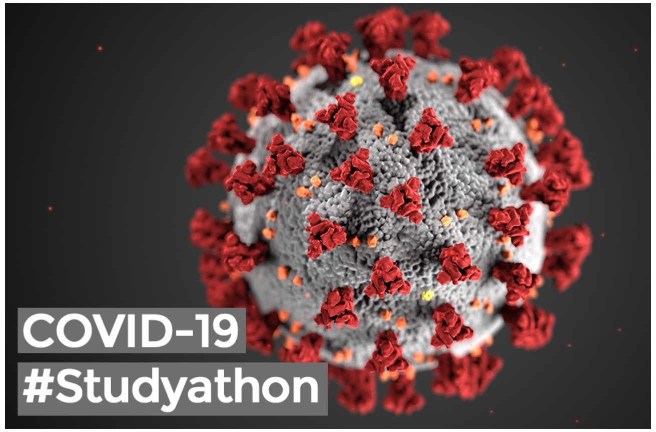
An FDA-Recognized Human Genetic Variant Database*

685	5697	127	107
Genes	Alterations	Cancer Types	Drugs

Level 1	Level 2	Level 3	Level 4	Level R1/R2
FDA-approved drugs	Standard care	Clinical evidence	Biological evidence	Resistance
43 Genes	20 Genes	26 Genes	24 Genes	11 Genes

https://www.nature.com/collections/ccigjichjc/

Our RWD research impact during COVID-19



OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

THE LANCET
Rheumatology

956,374 patient records

Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study

Jennifer C E Lane, James Weaver*, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F Abrahao, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Patricia Biedermann, Juan M Banda, Edward Burn, Paula Casajust, Mitchell M Conover, Aedin C Culhane, Alexander Davydov, Scott L DuVall, Dmitry Dymshyts, Sergio Fernandez-Bertolin, Kristina Fišter, Jill Hardin, Laura Hester, George Hripcsak, Benjamin Skov Kaas-Hansen, Seamus Kent, Sajan Khosla, Spyros Kolovos, Christophe G Lambert, Johan van der Lei, Kristine E Lynch, Rupa Makadia, Andrea V Margulis, Michael E Matheny, Paras Mehta, Daniel R Morales, Henry Morgan-Stewart, Mees Mosseveld, Danielle Newby, Fredrik Nyberg, Anna Ostropolets, Rae Woong Park, Albert Prats-Uribe, Gowtham A Rao, Christian Reich, Jenna Reps, Peter Rijnbeek, Selva Muthu Kumaran Sathappan, Martijn Schuemie, Sarah Seager, Anthony G Sena, Azza Shoaibi, Matthew Spotnitz, Marc A Suchard, Carmen O Torre, David Vizcaya, Haini Wen, Marcel de Wilde, Junqing Xie, Seng Chan You, Lin Zhang, Oleg Zhuk, Patrick Ryan, Daniel Prieto-Alhambra, on behalf of the OHDSI-COVID-19 consortium*

Lancet Rheumatol 2020; 2: e698–711

https://doi.org/10.1016/S2665-9913(20)30276-9

See Comment page e652

*Contributed equally

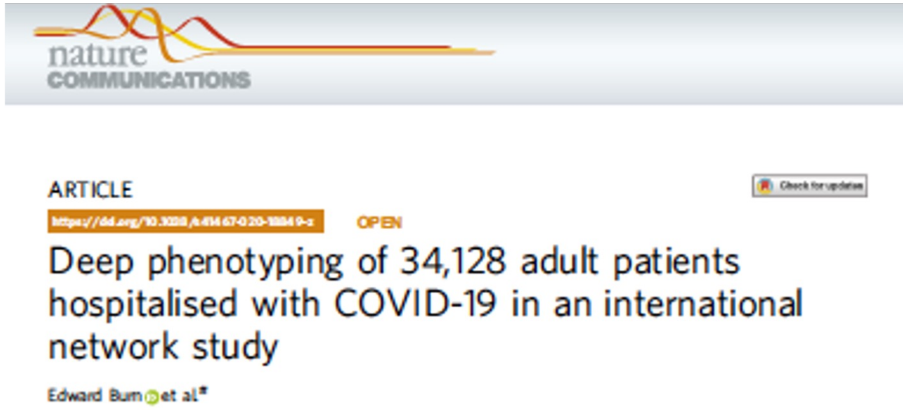
Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK (J C E Lane MRCS, E Burn MSc, S Kolovos PhD, A Prats-Uribe MPH, J Xie MSc, Prof D Prieto-Alhambra PhD); **Janssen Research and Development, Titusville, NJ, USA** (J Weaver MSc, M M Conover PhD, J Hardin PhD, L Hester PhD, R Makadia PhD, G A Rao MD, J Reps PhD, M Schuemie PhD, A G Sena BA, A Shoaibi PhD, P Ryan PhD); **Real World Solutions, IOVIA,**

Summary

Background Hydroxychloroquine, a drug commonly used in the treatment of rheumatoid arthritis, has received much negative publicity for adverse events associated with its authorisation for emergency use to treat patients with COVID-19 pneumonia. We studied the safety of hydroxychloroquine, alone and in combination with azithromycin, to determine the risk associated with its use in routine care in patients with rheumatoid arthritis.

Methods In this multinational, retrospective study, new user cohort studies in patients with rheumatoid arthritis aged 18 years or older and initiating hydroxychloroquine were compared with those initiating sulfasalazine and followed up over 30 days, with 16 severe adverse events studied. Self-controlled case series were done to further establish safety in wider populations, and included all users of hydroxychloroquine regardless of rheumatoid arthritis status or indication. Separately, severe adverse events associated with hydroxychloroquine plus azithromycin (compared with hydroxychloroquine plus amoxicillin) were studied. Data comprised 14 sources of claims data or electronic medical records from Germany, Japan, the Netherlands, Spain, the UK, and the USA. Propensity score stratification and calibration using negative control outcomes were used to address confounding. Cox models were fitted to estimate calibrated hazard ratios (HRs) according to drug use. Estimates were pooled where the I^2 value was less than 0·4.

Findings The study included 956 374 users of hydroxychloroquine, 310 350 users of sulfasalazine, 323 122 users of hydroxychloroquine plus azithromycin, and 351 956 users of hydroxychloroquine plus amoxicillin. No excess risk of severe adverse events was identified when 30-day hydroxychloroquine and sulfasalazine use were compared. Self-controlled case series confirmed these findings. However, long-term use of hydroxychloroquine appeared to be associated with increased cardiovascular mortality (calibrated HR 1·65 [95% CI 1·12–2·44]). Addition of azithromycin appeared to be associated with an increased risk of 30-day cardiovascular mortality (calibrated HR 2·19 [95% CI 1·22–3·95]), chest pain or angina (1·15 [1·05–1·26]), and heart failure (1·22 [1·02–1·45]).



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-18849-z OPEN

Check for updates

Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study

Edward Burn et al.*

CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION | RESEARCH ARTICLE

Characteristics and Outcomes of Over 300,000 Patients with COVID-19 and History of Cancer in the United States and Spain

Elena Roel[1,2], Andrea Pistillo[1], Martina Recalde[1,2], Anthony G. Sena[3,4], Sergio Fernández-Bertolín[1], Maria Aragón[1], Diana Puente[1,2], Waheed-Ul-Rahman Ahmed[5,6], Heba Alghoul[7], Osaid Alser[8], Thamir M. Alshammari[9], Carlos Areia[10], Clair Blacketer[3], William Carter[11], Paula Casajust[12], Aedin C. Culhane[13,14], Dalia Dawoud[15], Frank DeFalco[3], Scott L. DuVall[16,17], Thomas Falconer[18,19], Asieh Golozar[20,21], Mengchun Gong[22], Laura Hester[23], George Hripcsak[18,19], Eng Hooi Tan[24], Hokyun Jeon[25], Jitendra Jonnagaddala[26], Lana Y.H. Lai[27], Kristine E. Lynch[16,17], Michael E. Matheny[28,29], Daniel R. Morales[30,31], Karthik Natarajan[18,19], Fredrik Nyberg[32], Anna Ostropolets[18], José D. Posada[33], Albert Prats-Uribe[24], Christian G. Reich[34], Donna R. Rivera[35], Lisa M. Schilling[11], Isabelle Soerjomataram[36], Karishma Shah[5], Nigam H. Shah[33], Yang Shen[22], Matthew Spotniz[18], Vignesh Subbian[37], Marc A. Suchard[38], Annalisa Trama[39], Lin Zhang[40,41], Ying Zhang[22], Patrick B. Ryan[3,18], Daniel Prieto-Alhambra[24], Kristin Kostka[34], and Talita Duarte-Salles[1]

Hydroxychloroquine and COVID-19

- From March 1 to April 30, 2020, Donald J Trump made 11 tweets about unproven therapies and mentioned these therapies 65 times in White House briefings, especially touting hydroxychloroquine and chloroquine

HEALTH AND SCIENCE

Trump says he still thinks hydroxychloroquine works in t early stage coronavirus

PUBLISHED TUE, JUL 28 2020·5:49 PM EDT | UPDATED WED, JUL 29 2020·11:22 AM EDT

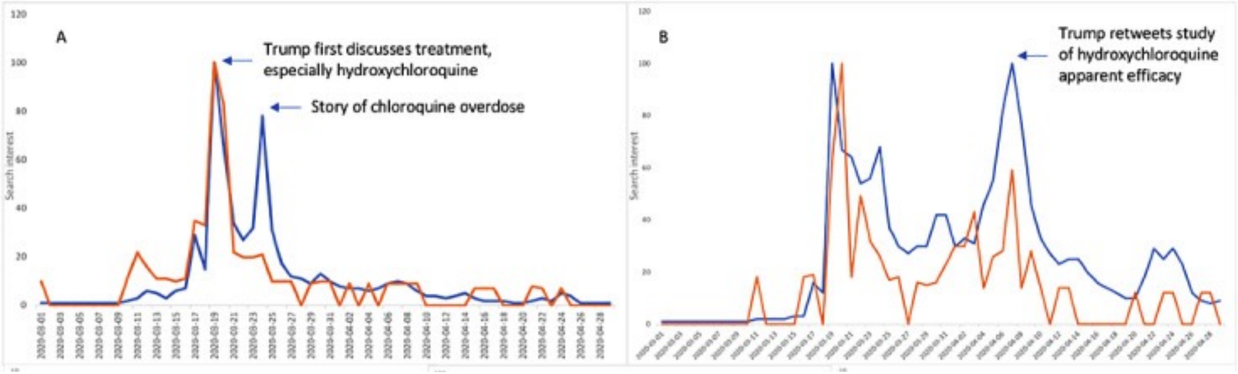
Berkeley Lovelace Jr.
@BERKELEYJR

KEY POINTS

- Trump was asked about a video he shared on Twitter that went viral across social media platforms that claimed hydroxychloroquine is "a cure for Covid."
- The video was later labeled as containing misleading information and has since been taken down.
- There are no FDA-approved drugs for the coronavirus, which has infected more than 16 million people worldwide and killed at least 655,300.

VIDEO 02:41

Trump: I happen to believe in hydroxychloroquine



Google searches (blue line) Purchases (orange line)

[J Med Internet Res. 2020 Nov; 22(11): e20044.](#)

Safety of hydroxychloroquine

- Evidence was needed around the use of hydroxychloroquine (HCQ) alone and in combination with azithromycin (AZ). We examined the use of these drugs in rheumatoid arthritis (RA) patients.
- Findings:
  - In history use in RA population, HCQ alone is generally safe but in combination with AZ it shows a doubling of risk of 30-day cardiovascular mortality.

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Study-a-thon
March 26-29th

Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study

Initial draft
April 10th 2020

COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine

News 23/04/2020

Chloroquine and hydroxychloroquine are known to potentially cause heart rhythm problems, and these could be exacerbated if treatment is combined with other medicines, such as the antibiotic azithromycin, that have similar effects on the heart.

Recent studies[1,2] have reported serious, in some cases fatal, heart rhythm problems with chloroquine or hydroxychloroquine, particularly when taken at high doses or in combination with the antibiotic azithromycin.

April 23rd 2020

ARTICLES | VOLUME 2, ISSUE 11, E698-E711, NOVEMBER 01, 2020

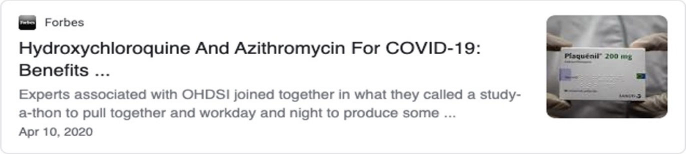
Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study

Jennifer C E Lane, MRCS † • James Weaver, MSc † • Kristin Kostka, MPH • Talita Duarte-Salles, PhD • Maria Tereza F Abrahao, PhD • Heba Alghoul, MD • et al.

Open Access • Published: August 21, 2020 • DOI: https://doi.org/10.1016/S2665-9913(20)30276-9

Aug 21st 2020

EMA Recommendation
REAL WORLD IMPACT FROM RWD

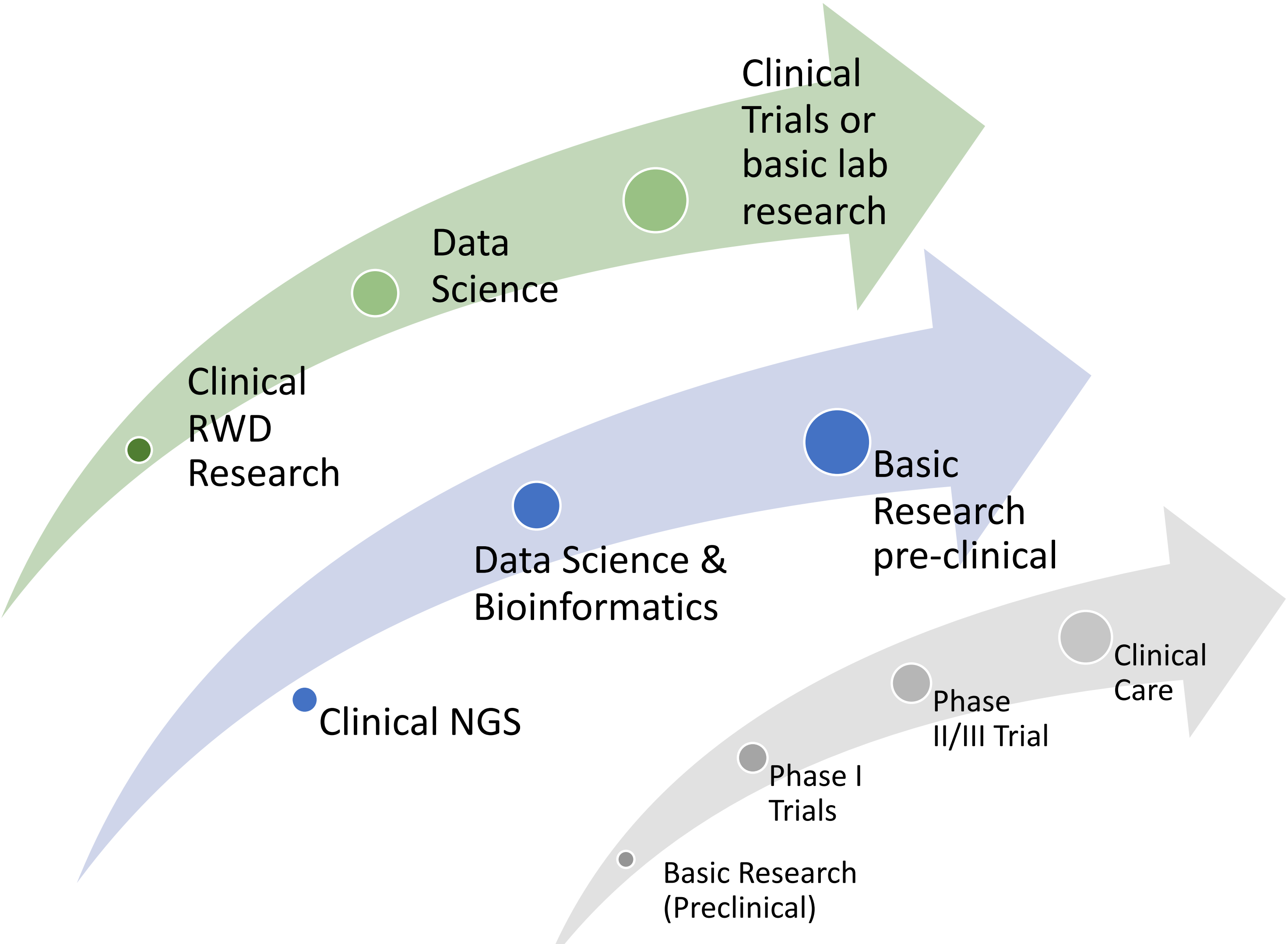


Hydroxychloroquine And Azithromycin For COVID-19: Benefits ...

Experts associated with OHDSI joined together in what they called a study-a-thon to pull together and workday and night to produce some ...

Apr 10, 2020

Data Driven Clinical Oncology Research



Clinical RWD Research

Data Science

Clinical Trials or basic lab research

Clinical NGS

Data Science & Bioinformatics

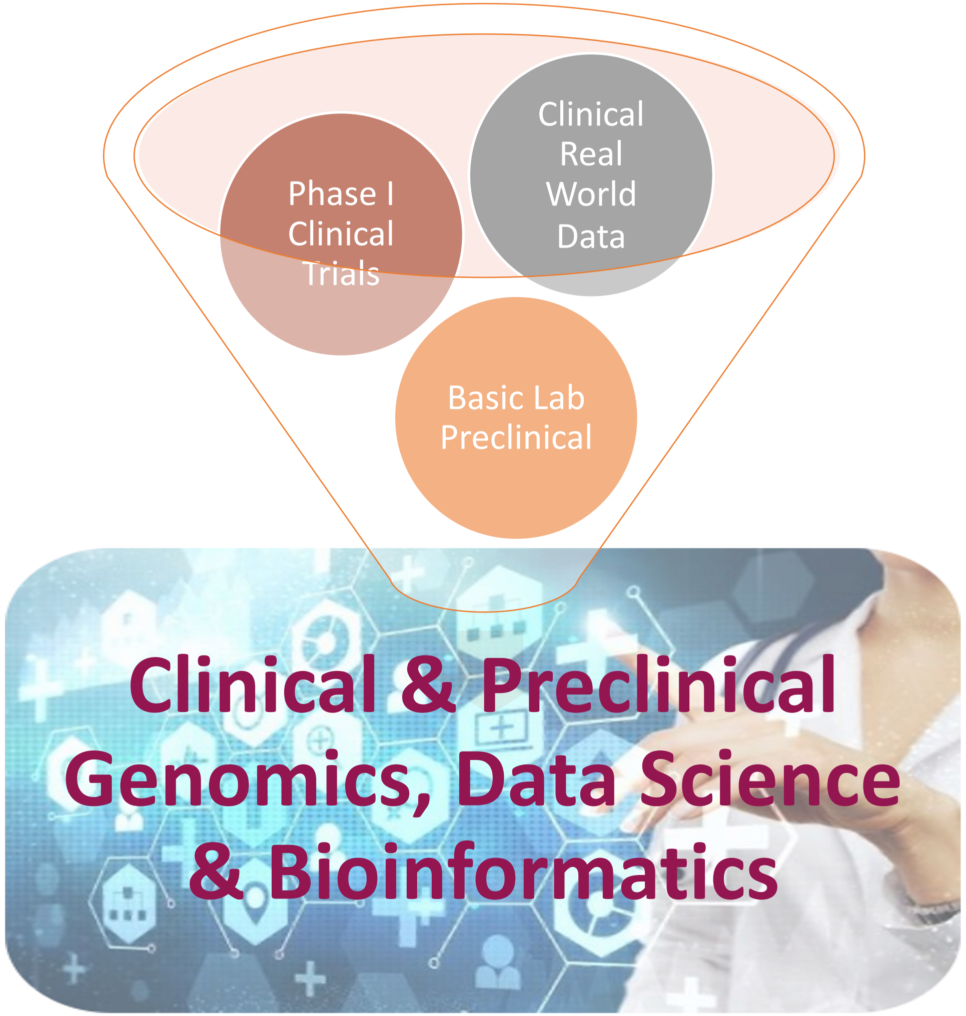
Basic Research pre-clinical

Basic Research (Preclinical)

Phase I Trials

Phase II/III Trial

Clinical Care



Phase I Clinical Trials

Clinical Real World Data

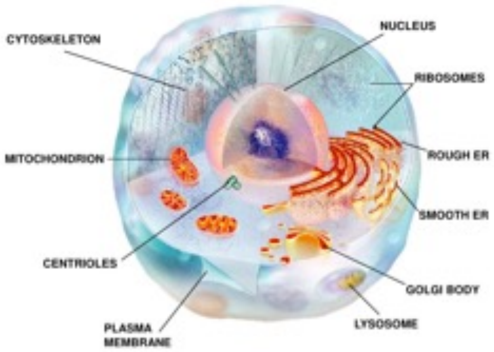
Basic Lab Preclinical

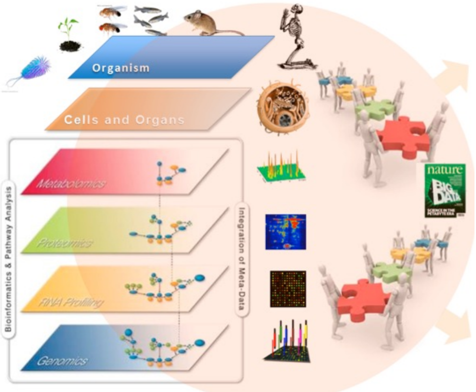
Clinical & Preclinical Genomics, Data Science & Bioinformatics

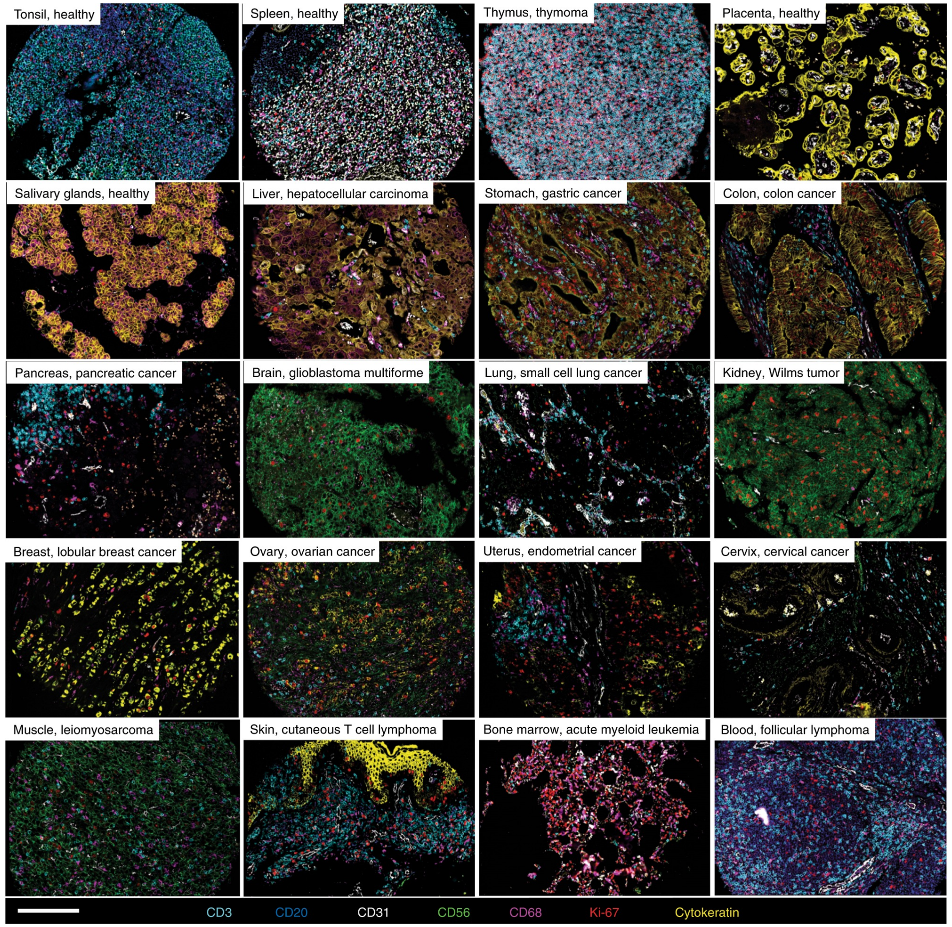
Culhane lab- Computational Oncology model that integrate multi modal data

2557.MacDonald
2558.Macduff
2559.Macey
2560.Mackenzie
2561.Mansfield
2562.Marlow
2563.Marshman
2564.Mason

Diseases:
Family history:
Habbits:







Complexity of cancer : molecular basis of multicellular disease

- Human disease occurs within a complex milieu of cells
- Multiple body systems are involved in disease response;

  immune, lymph, nervous, endocrine
- Disease response involves local and systemic signalling and local tissue effects
- Harnessing the immune system

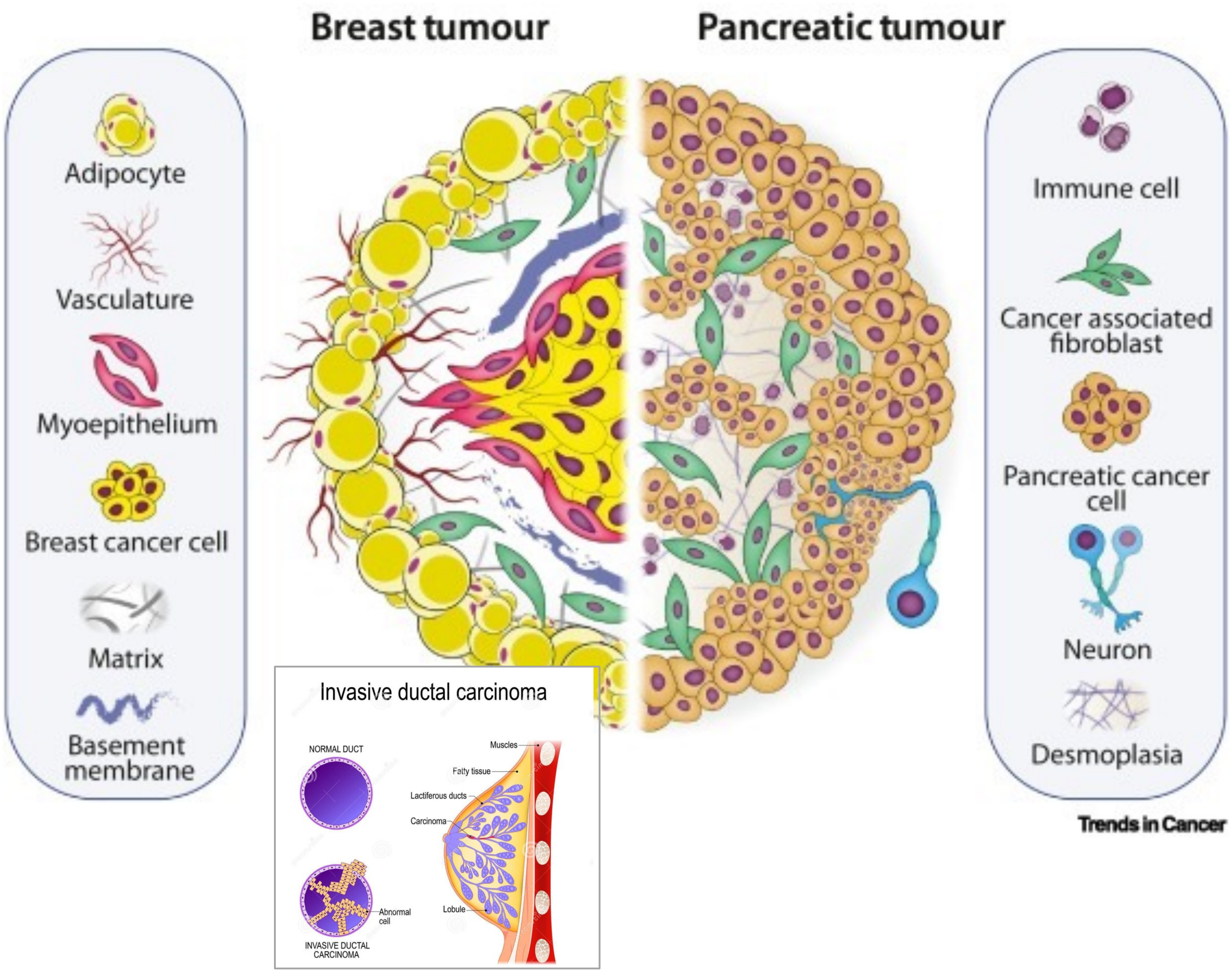
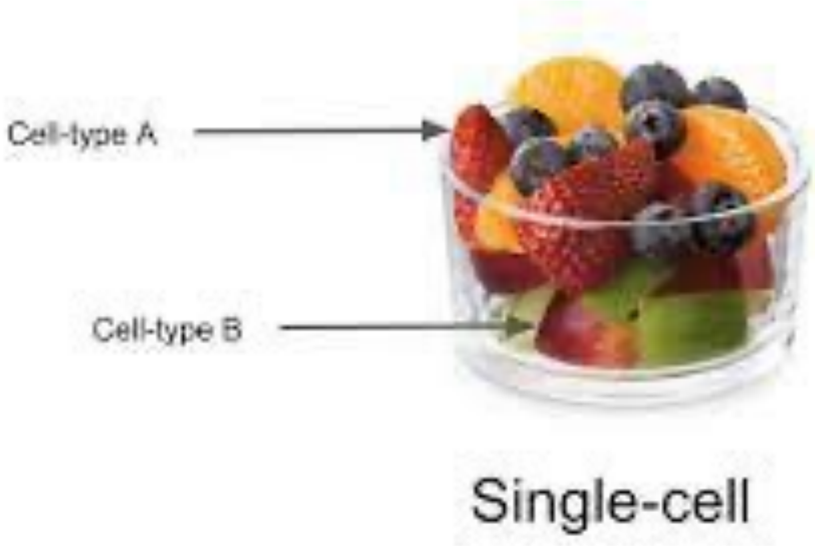


Figure from Carter et al., 2021, Trends in Cancer 7:11

Tremendous Technology Advances in <5 years



Average of cell mixture biopsy (pre-2020)

Spatial single cell measurements (post 2020)

Immunity

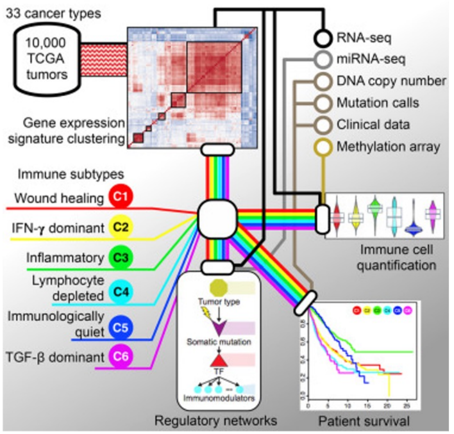
Volume 48, Issue 4, 17 April 2018, Pages 812-830.e14

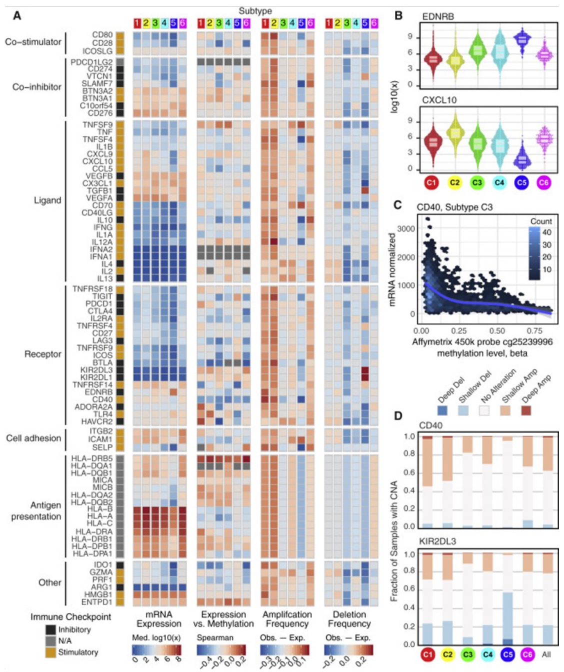
CellPress

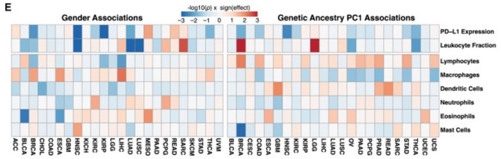
Resource

The Immune Landscape of Cancer

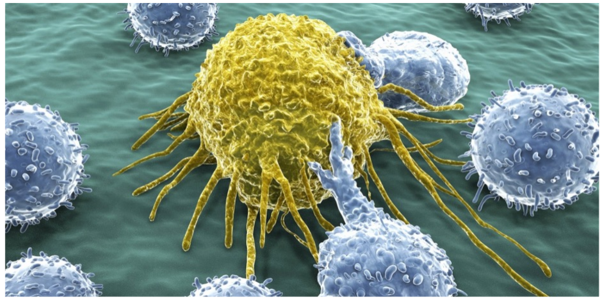
Vésteinn Thorsson[1, 37], David L. Gibbs[1, 36], Scott D. Brown[2], Denise Wolf[3], Dante S. Bortone[4], Tai-Hsien Ou Yang[5], Eduard Porta-Pardo[6, 7], Galen F. Gao[8], Christopher L. Plaisier[1, 9], James A. Eddy[10], Elad Ziv[11], Aedin C. Culhane[12], Evan O. Paull[13], I.K. Ashok Sivakumar[14], Andrew J. Gentles[15], Raunaq Malhotra[16], Farshad Farshidfar[17], Antonio Colaprico[18] … Ilya Shmulevich[1]

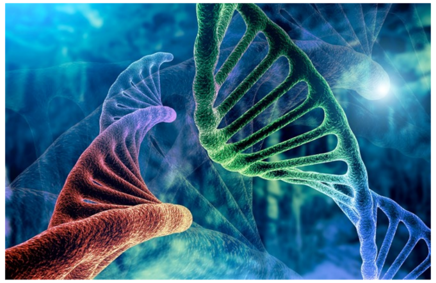


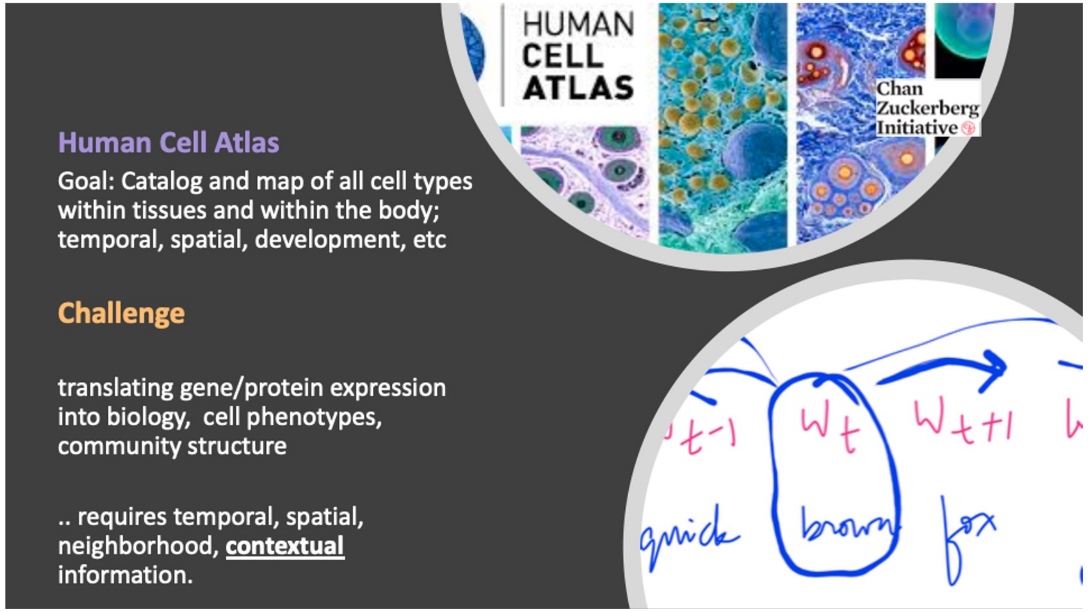




> 10,000 tumors comprising 33 diverse cancer types (TCGA). Across 6 immune types pan-cancers







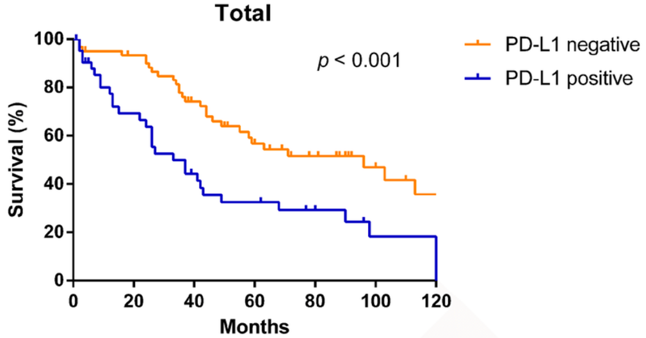
Human Cell Atlas

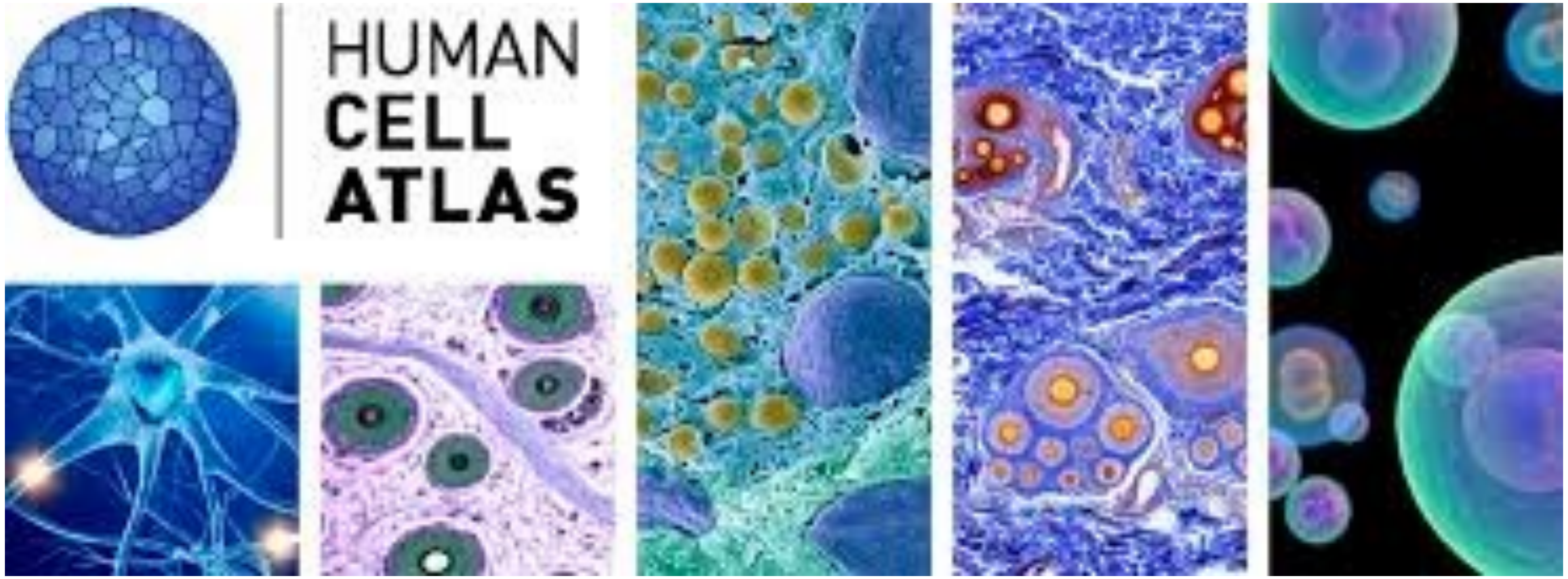
Goal: Catalog and map of all cell types within tissues and within the body; temporal, spatial, development, etc

Challenge

translating gene/protein expression into biology, cell phenotypes, community structure

.. requires temporal, spatial, neighborhood, **contextual** information.





Creating a Human Cell Atlas

catalog and map of all cell types to the location within tissues and within the body; temporal, spatial, development

Chan
Zuckerberg
Initiative

Research Topic

Multi-omic Data Integration in Oncology

Submission closed.

Overview

13 Articles

Articles

By Views By Type By Date

Impact of Data Preprocessing on Integrative Matrix Factorization of Single Cell Data

Lauren L. Hsu and Aedin C. Culhane

Mini Review Integrative, single-cell analyses may provide unprecedented insights into cellular and spatial diversity of the tumor microenvironment. The sparsity, noise, and high dimensionality of these data present unique challenges. Whilst approaches for ...

Published on 23 June 2020

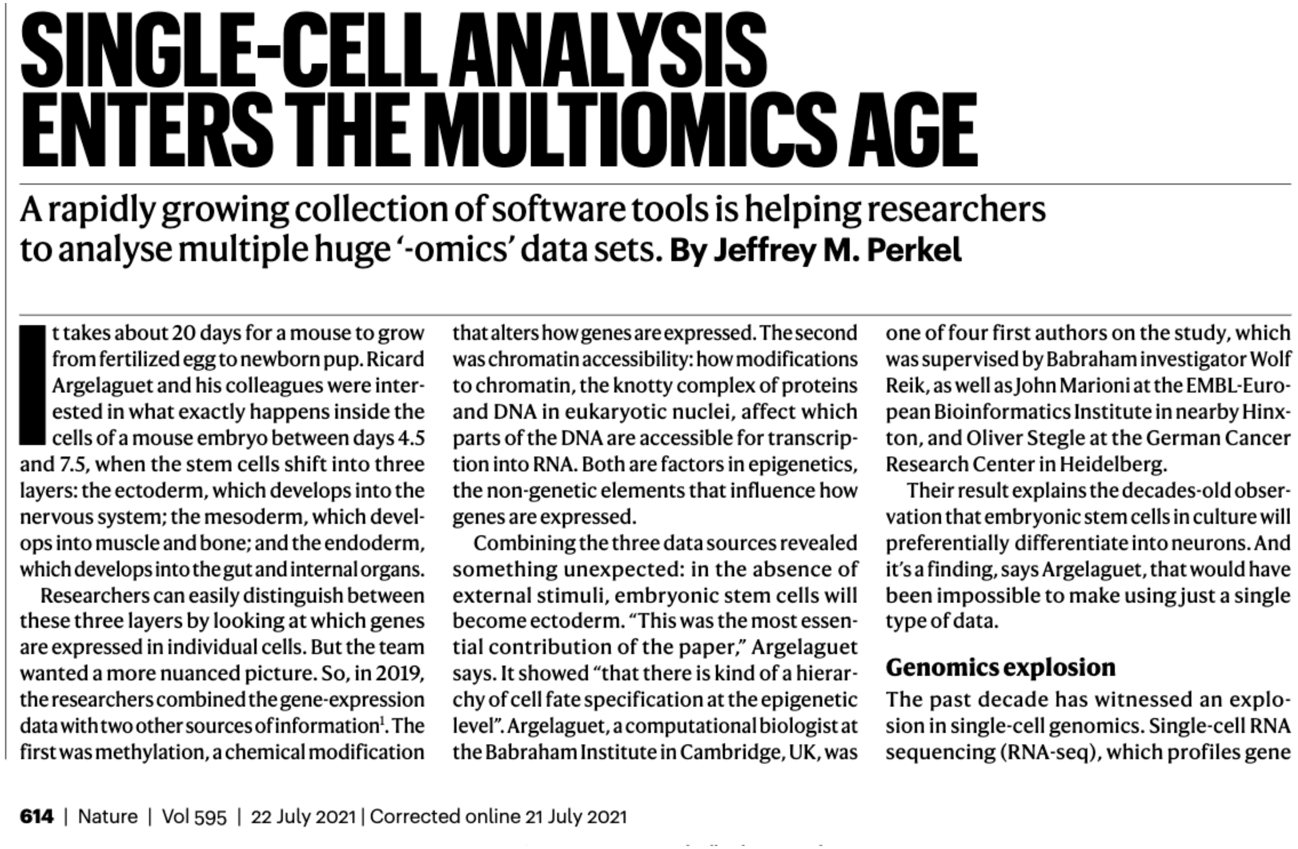
Front. Oncol. doi: 10.3389/fonc.2020.00973

3,467 total views Altmetric 102

frontiers in Oncology | Cancer Genetics

corral

Hsu & Culhane **corral: Single-cell RNA-seq dimension reduction, batch integration, and visualization with correspondence analysis** bioRxiv 2021.11.24.469874;



SINGLE-CELL ANALYSIS ENTERS THE MULTIOMICS AGE

A rapidly growing collection of software tools is helping researchers to analyse multiple huge '-omics' data sets. **By Jeffrey M. Perkel**

It takes about 20 days for a mouse to grow from fertilized egg to newborn pup. Ricard Argelaguet and his colleagues were interested in what exactly happens inside the cells of a mouse embryo between days 4.5 and 7.5, when the stem cells shift into three layers: the ectoderm, which develops into the nervous system; the mesoderm, which develops into muscle and bone; and the endoderm, which develops into the gut and internal organs.

Researchers can easily distinguish between these three layers by looking at which genes are expressed in individual cells. But the team wanted a more nuanced picture. So, in 2019, the researchers combined the gene-expression data with two other sources of information[1]. The first was methylation, a chemical modification that alters how genes are expressed. The second was chromatin accessibility: how modifications to chromatin, the knotty complex of proteins and DNA in eukaryotic nuclei, affect which parts of the DNA are accessible for transcription into RNA. Both are factors in epigenetics, the non-genetic elements that influence how genes are expressed.

Combining the three data sources revealed something unexpected: in the absence of external stimuli, embryonic stem cells will become ectoderm. "This was the most essential contribution of the paper," Argelaguet says. It showed "that there is kind of a hierarchy of cell fate specification at the epigenetic level". Argelaguet, a computational biologist at the Babraham Institute in Cambridge, UK, was one of four first authors on the study, which was supervised by Babraham investigator Wolf Reik, as well as John Marioni at the EMBL-European Bioinformatics Institute in nearby Hinxton, and Oliver Stegle at the German Cancer Research Center in Heidelberg.

Their result explains the decades-old observation that embryonic stem cells in culture will preferentially differentiate into neurons. And it's a finding, says Argelaguet, that would have been impossible to make using just a single type of data.

Genomics explosion

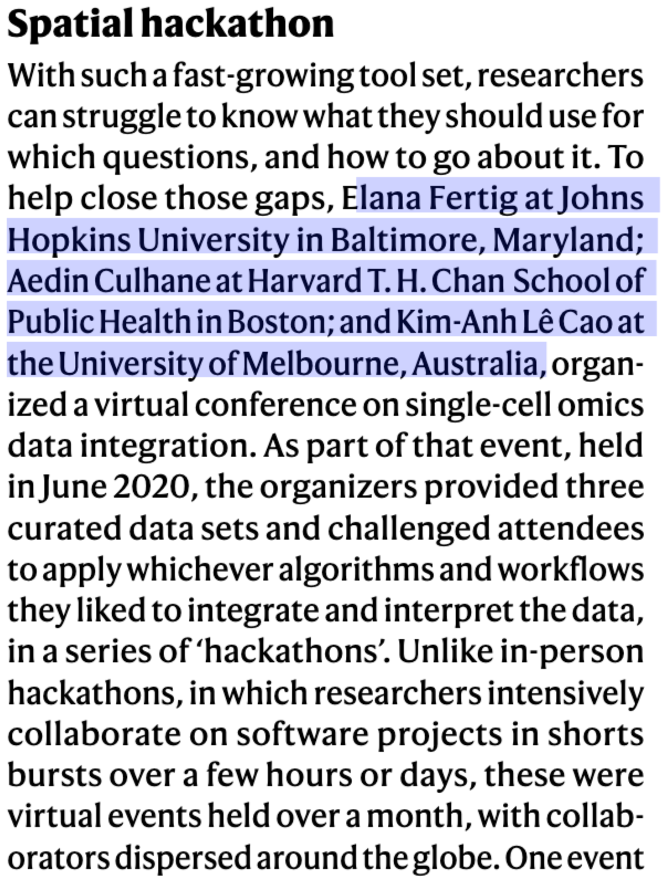
The past decade has witnessed an explosion in single-cell genomics. Single-cell RNA sequencing (RNA-seq), which profiles gene

https://www.nature.com/articles/d41586-021-01994-w

Aedín Culhane
Dana-Farber
Cancer Institute/
Harvard Chan

Elana Fertig
Johns Hopkins
University

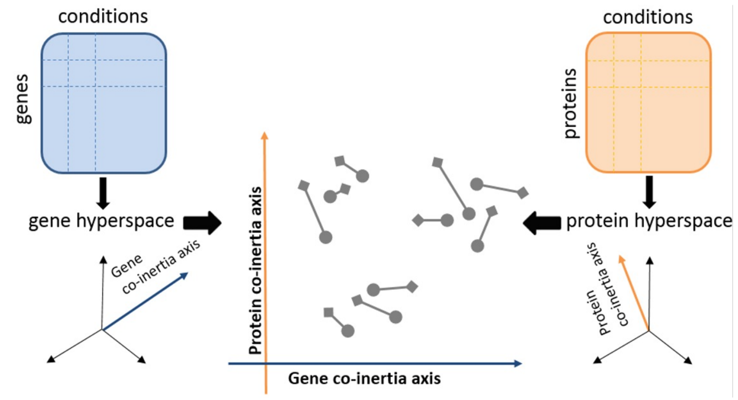
Kim-Anh Lê Cao
The University of
Melbourne

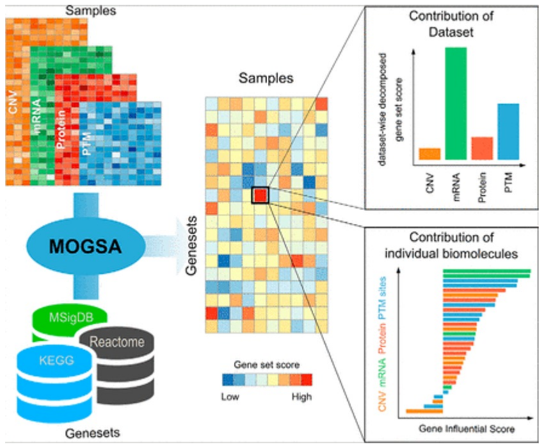


Spatial hackathon

With such a fast-growing tool set, researchers can struggle to know what they should use for which questions, and how to go about it. To help close those gaps, Elana Fertig at Johns Hopkins University in Baltimore, Maryland; Aedin Culhane at Harvard T. H. Chan School of Public Health in Boston; and Kim-Anh Lê Cao at the University of Melbourne, Australia, organized a virtual conference on single-cell omics data integration. As part of that event, held in June 2020, the organizers provided three curated data sets and challenged attendees to apply whichever algorithms and workflows they liked to integrate and interpret the data, in a series of 'hackathons'. Unlike in-person hackathons, in which researchers intensively collaborate on software projects in shorts bursts over a few hours or days, these were virtual events held over a month, with collaborators dispersed around the globe. One event

Culhane lab- Multi Modal, Multivariate analysis Matrix Factorization





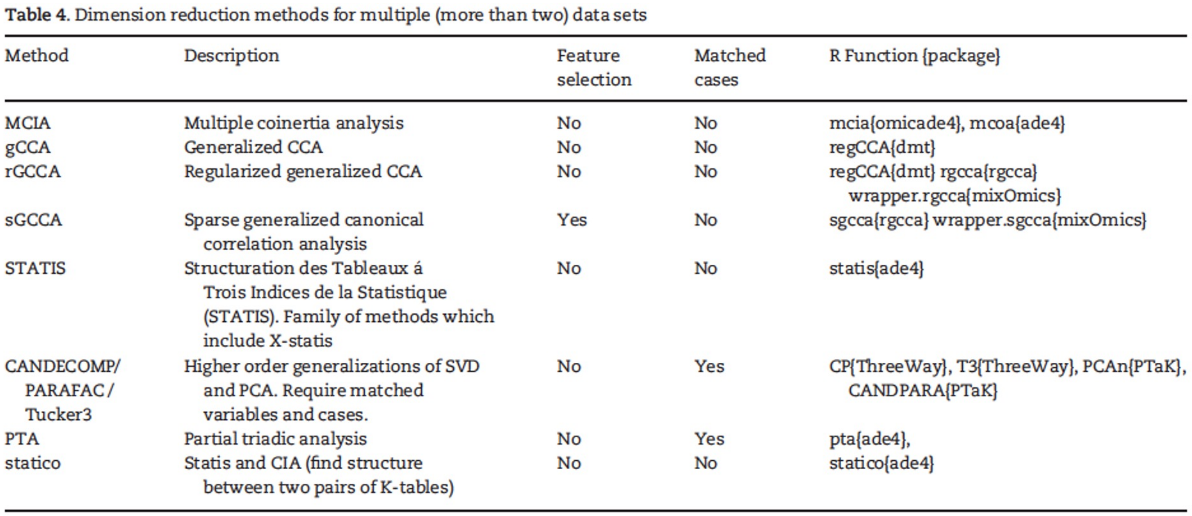
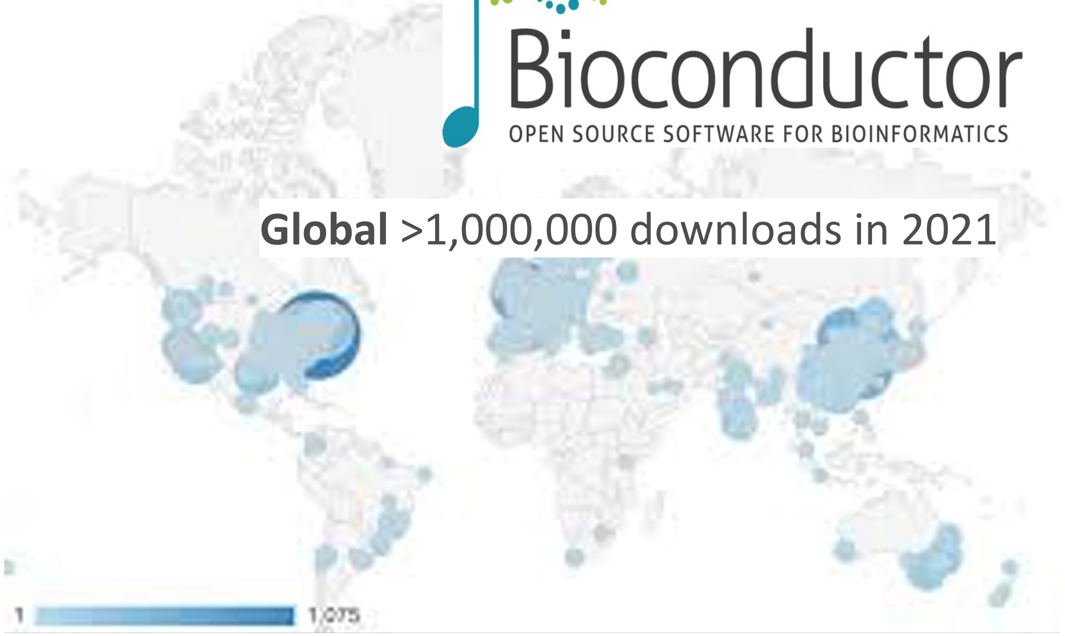


Table 4. Dimension reduction methods for multiple (more than two) data sets

Method	Description	Feature selection	Matched cases	R Function {package}
MCIA	Multiple coinertia analysis	No	No	mcia{omicade4}, mcoa{ade4}
gCCA	Generalized CCA	No	No	regCCA{dmt}
rGCCA	Regularized generalized CCA	No	No	regCCA{dmt} rgcca{rgcca} wrapper.rgcca{mixOmics}
sGCCA	Sparse generalized canonical correlation analysis	Yes	No	sgcca{rgcca} wrapper.sgcca{mixOmics}
STATIS	Structuration des Tableaux á Trois Indices de la Statistique (STATIS). Family of methods which include X-statis	No	No	statis{ade4}
CANDECOMP/ PARAFAC / Tucker3	Higher order generalizations of SVD and PCA. Require matched variables and cases.	No	Yes	CP{ThreeWay}, T3{ThreeWay}, PCAn{PTaK}, CANDPARA{PTaK}
PTA	Partial triadic analysis	No	Yes	pta{ade4},
statico	Statis and CIA (find structure between two pairs of K-tables)	No	No	statico{ade4}

Bioconductor
OPEN SOURCE SOFTWARE FOR BIOINFORMATICS



Global >1,000,000 downloads in 2021

corral

mogsa

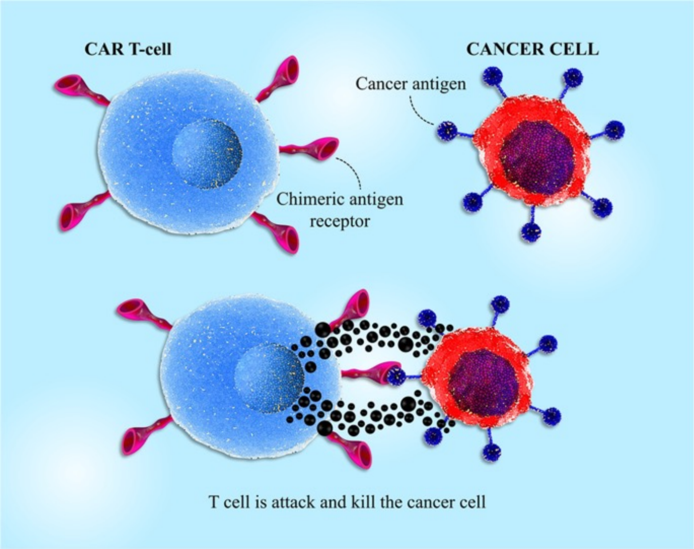
Overview of talk

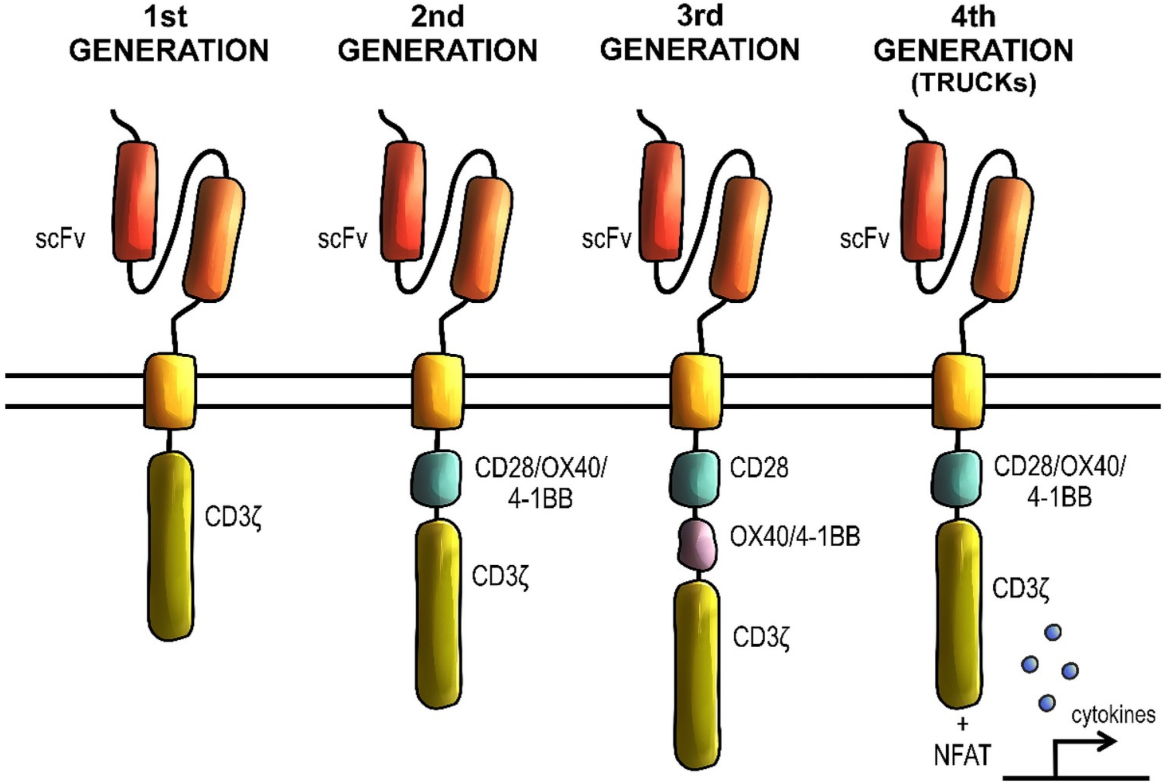
- Briefly introduce computational oncology and our lab

- **Two recent papers**
    - **CAR T-Cell in renal cancer**
    - **Sensitivity to NK cell killing**
    - **GVHD and tissue resident cells**

- eHealth -Hub for Cancer

Next generation CAR T-Cells therapies





Recognizes Tumor Antigen

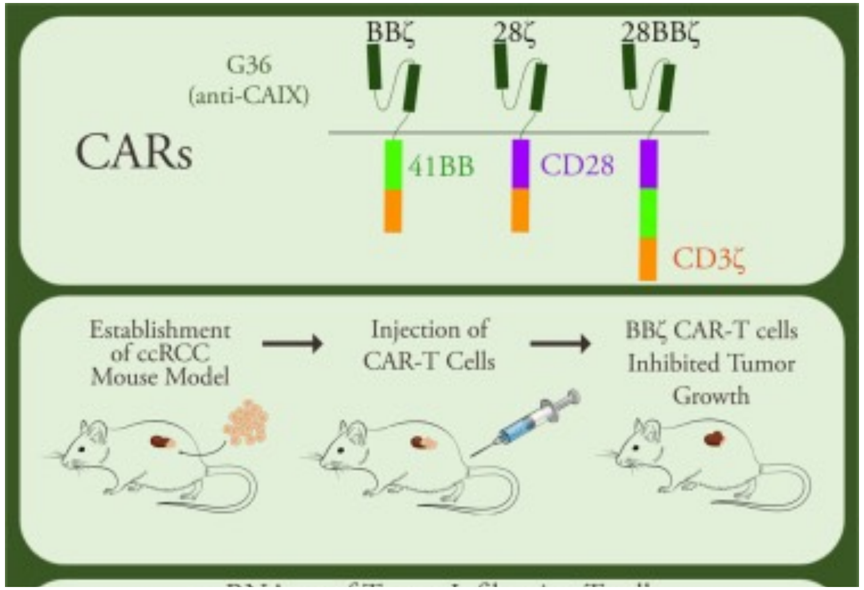
Attacks Tumor (Signalling)

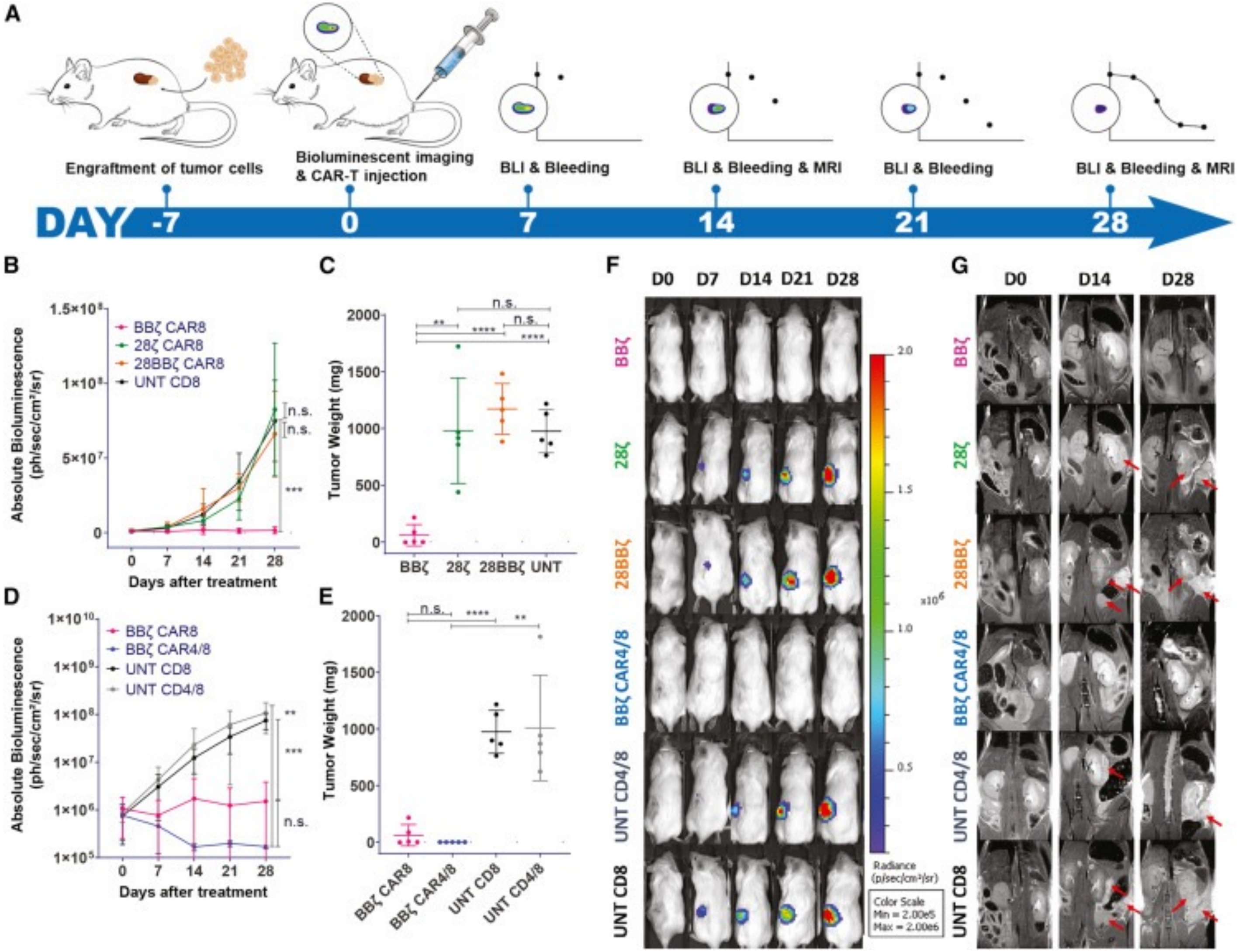
The most frequently used intracellular domains are derived from
- The CD28 family (CD28 and ICOS)
- The TNF receptor family (4-1BB, CD27, and OX40).

Molecular Therapy
Oncolytics
Original Article

Anti-CAIX BBζ CAR4/8 T cells exhibit superior efficacy in a ccRCC mouse model

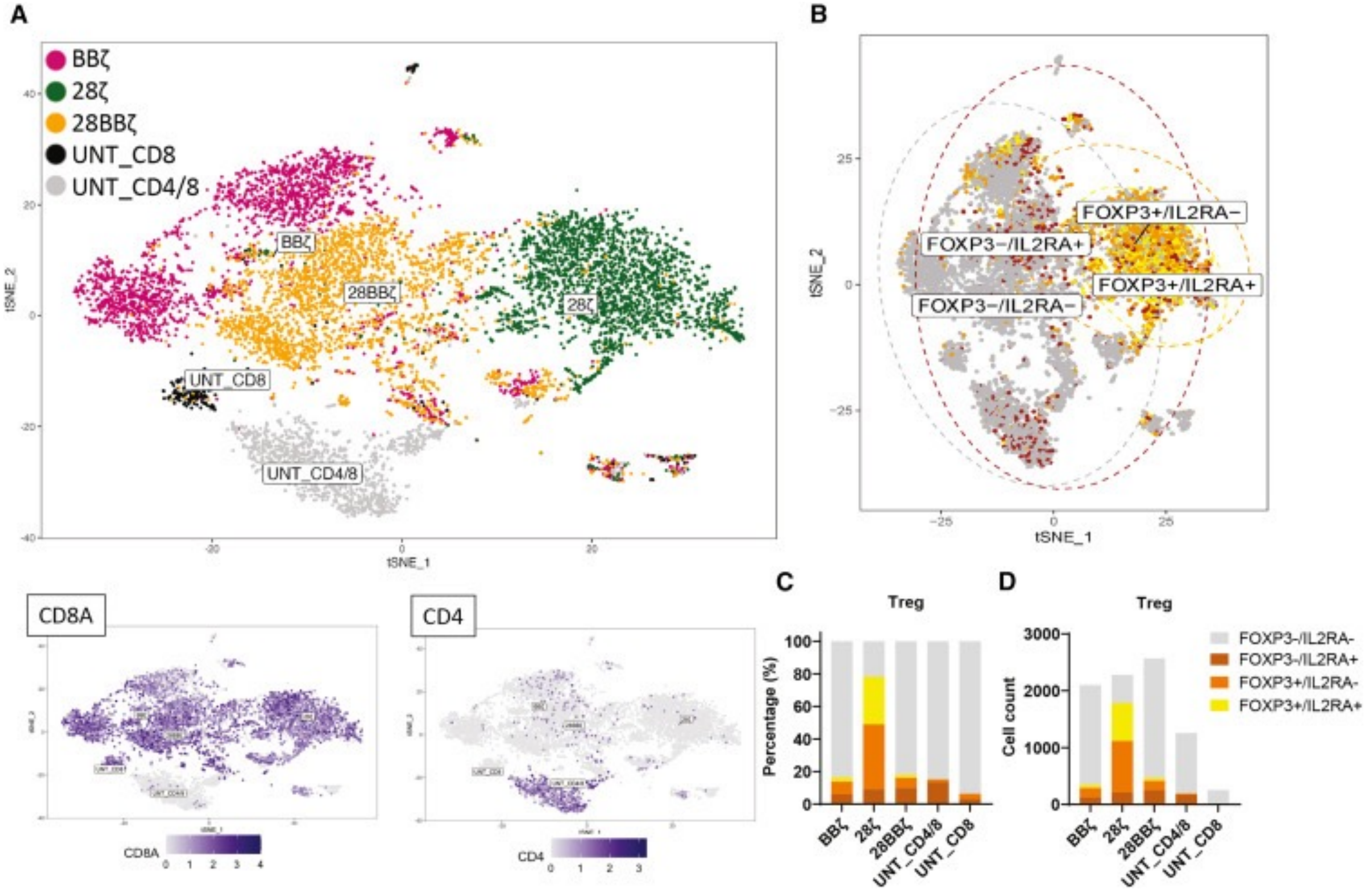
Yufei Wang,[1,2] Alicia Buck,[1] Marion Grimaud,[1] Aedin C. Culhane,[3,4,5] Sreekumar Kodangattil,[1] Cecile Razimbaud,[1] Dennis M. Bonal,[6] Quang-De Nguyen,[6] Zhu Zhu,[2,7] Kevin Wei,[2,7] Madison L. O'Donnell,[8] Ying Huang,[8] Sabina Signoretti,[2,8,9] Toni K. Choueiri,[2,10] Gordon J. Freeman,[2,10] Quan Zhu,[1,2] and Wayne A. Marasco[1,2]

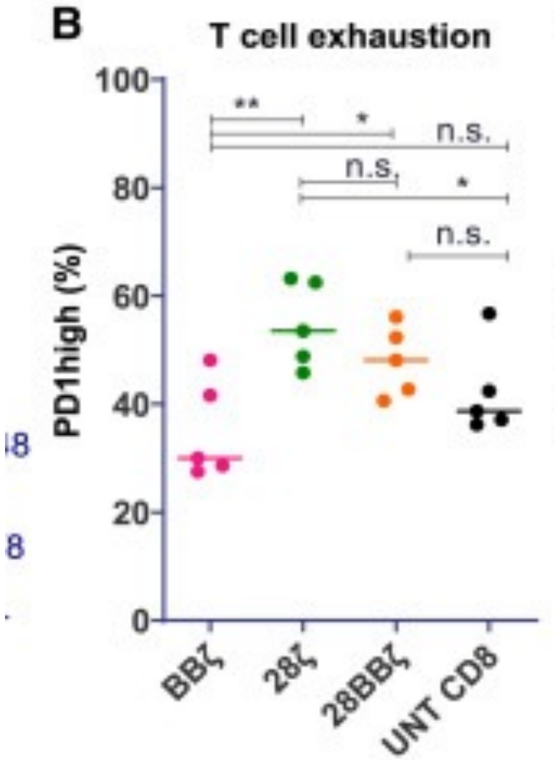


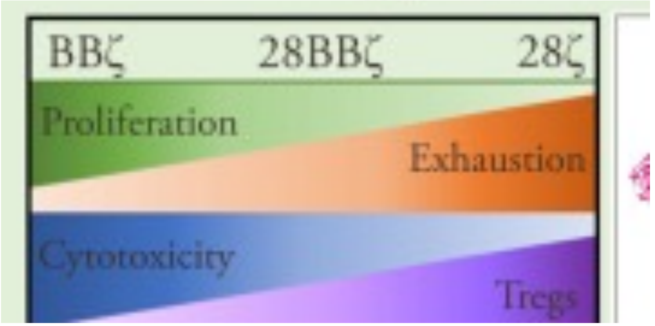


No 1st-generation CARs (poor persistence in vivo)
2nd -generation (28z and BBz) CARs
3rd-generation CAR (28BBz)

scRNAseq comparing 2^{nd}, 3^{rd} Generation CAR T-Cells therapies in ccRCC





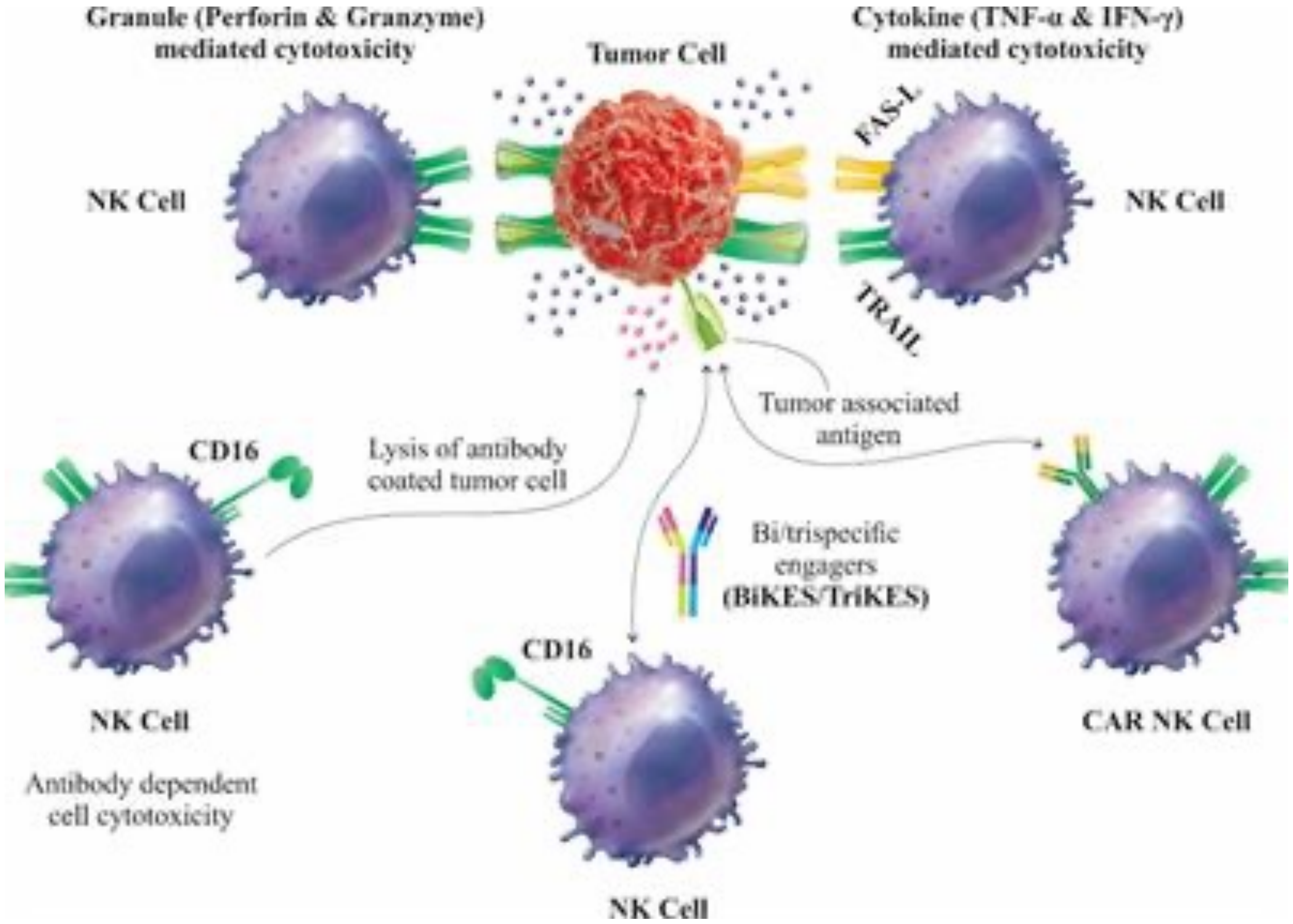


2. Towards NK cell therapy

Rapidly evolving interest in engineered NK cells for tumor immunotherapy

“infusions of allogeneic NK cells can be safely performed across human leukocyte antigen (HLA) barriers and avoid the graft-versus-host reactions that are an inherent challenge for immunotherapies based on administration of allogeneic T cells”

Scheffer et al., 2021 Nat Genet. 2021 Aug;53(8):1196-1206.



NK Cell Killing

ARTICLES

https://doi.org/10.1038/s41588-021-00889-w

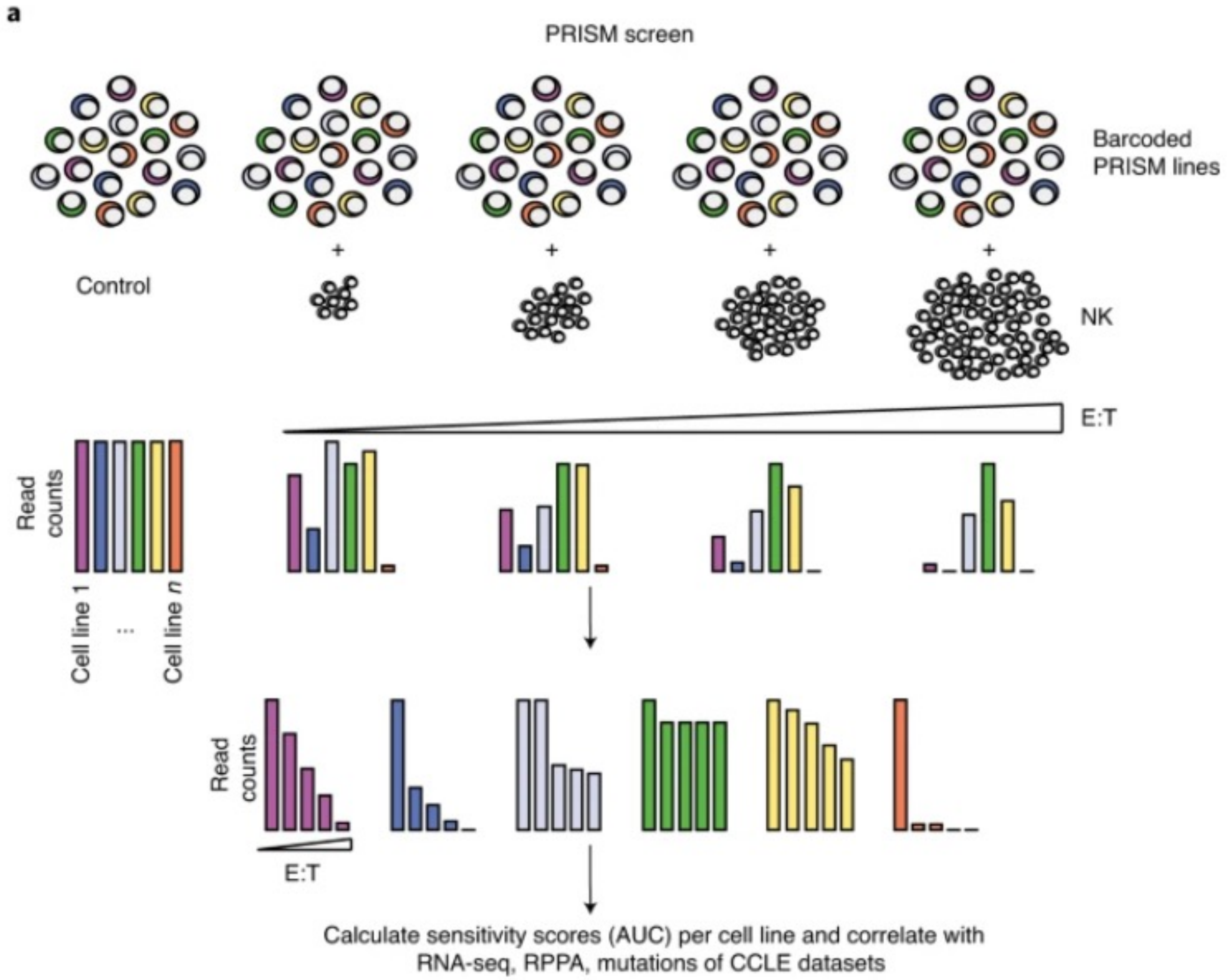
nature genetics

Check for updates

Genome-scale screens identify factors regulating tumor cell responses to natural killer cells

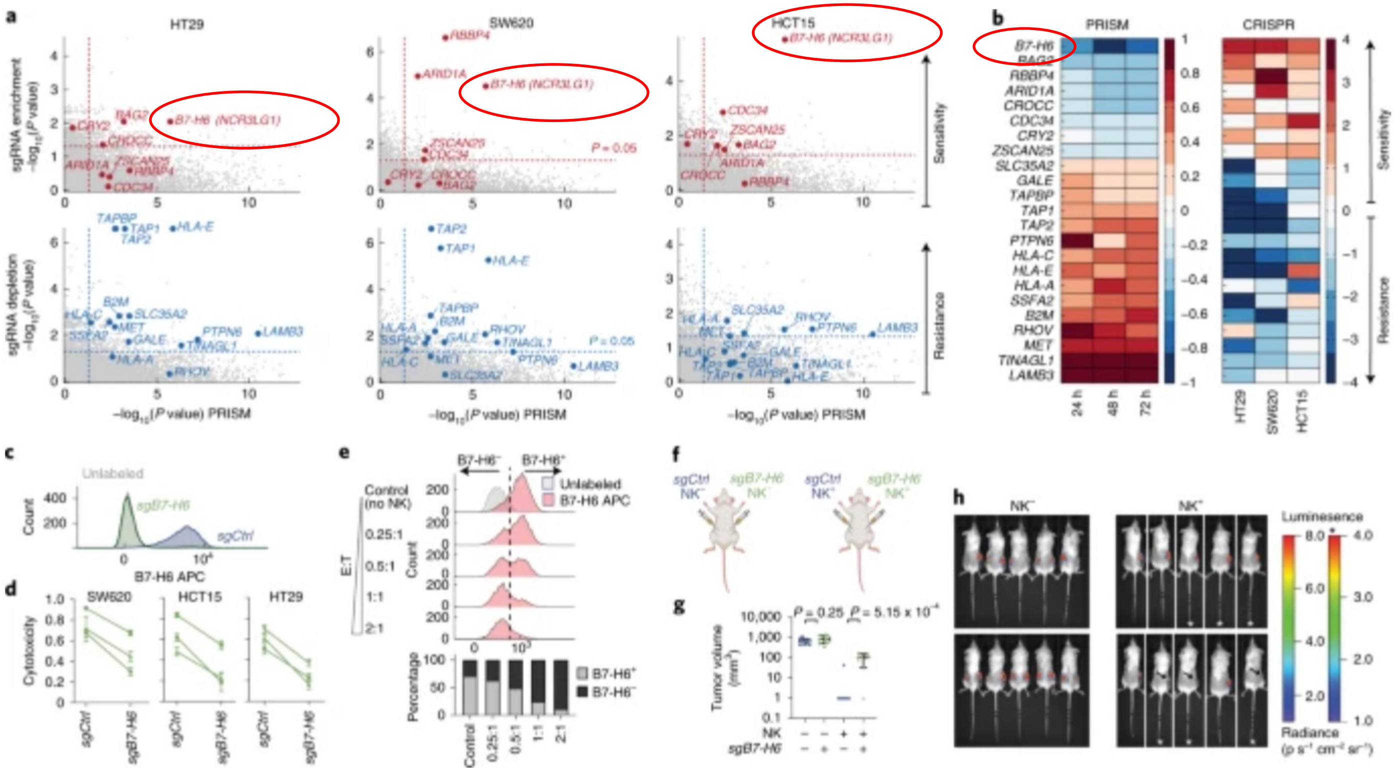
Michal Sheffer[1,2,3,4] ✉, Emily Lowry[1], Nicky Beelen[5,6], Minasri Borah[1], Suha Naffar-Abu Amara[7], Chris C. Mader[3], Jennifer A. Roth[3], Aviad Tsherniak[3], Samuel S. Freeman[3], Olga Dashevsky[1,2,3,4], Sara Gandolfi[1,2,3,4], Samantha Bender[3], Jordan G. Bryan[3], Cong Zhu[3], Li Wang[3], Ifrah Tariq[3,8], Govinda M. Kamath[9], Ricardo De Matos Simoes[1,2,3,4], Eugen Dhimolea[1,2,3,4], Channing Yu[1,2,3], Yiguo Hu[1,15], Olli Dufva[10,11,12], Marios Giannakis[1,2,3], Vasilis Syrgkanis[9], Ernest Fraenkel[3,8], Todd Golub[1,3], Rizwan Romee[1,2], Satu Mustjoki[10,11,12], Aedin C. Culhane[13,14], Lotte Wieten[5,6] and Constantine S. Mitsiades[1,2,3,4] ✉

Fig. 1: Overview of the PRISM study using NK cells.



B7H6 is essential for NK cell killing

Fig. 4: Key regulators of tumor cell responses to NK cells in PRISM and CRISPR studies.

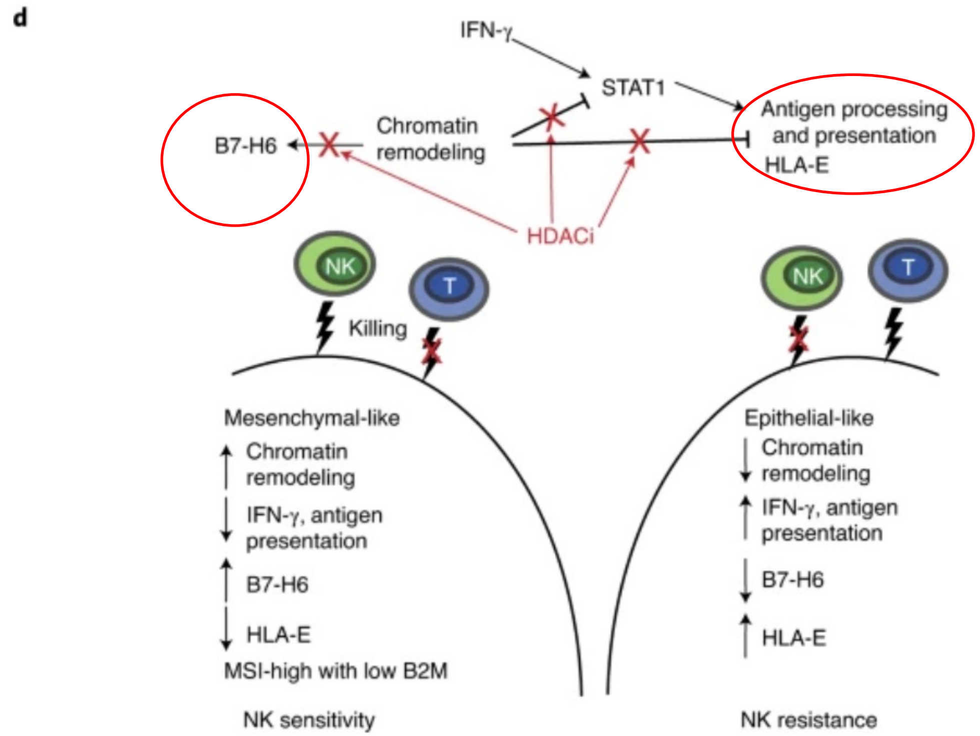


High B7H6 important for NK killing sensitivity

Tumor Immune Environment –NK cells

NK cell sensitive tumor cells

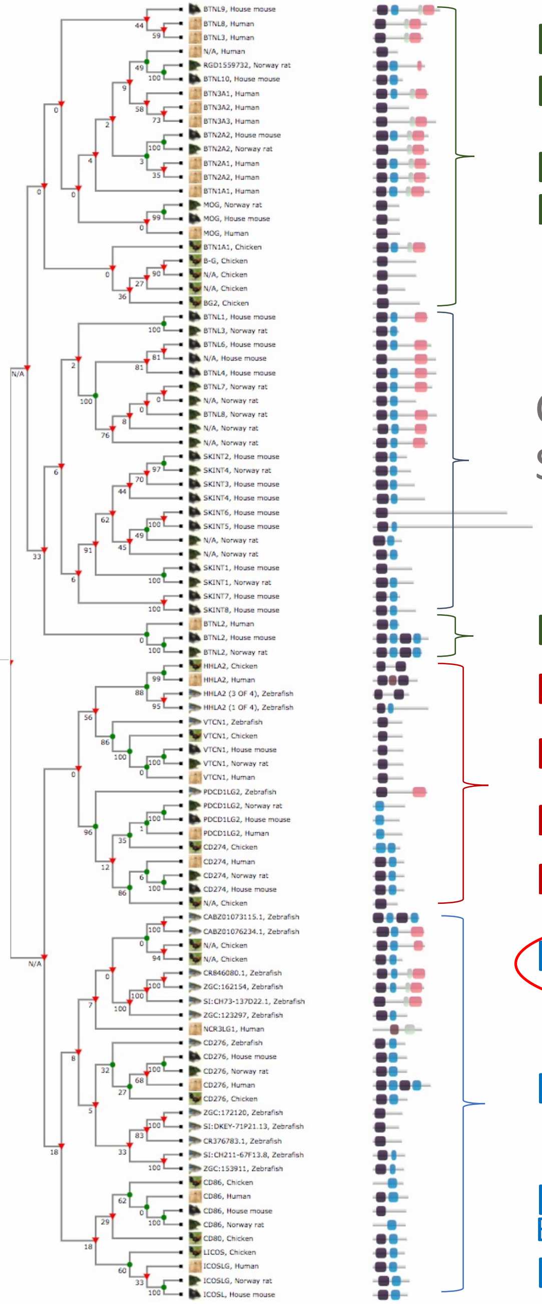
- chromatin remodeling
- ‘mesenchymal-like’ transcriptional programs
- high *B7-H6* (*NCR3LG1*)
- low levels of *HLA-E*/antigen presentation genes.
- NK cell–sensitive tumor cells correlate with immune checkpoint inhibitor (ICI) resistance in clinical samples.



PDL1/PDL2 family (treefam TF331083)

B7H6 is a B7 protein

In the same family as PD-1, and CTLA4



BTN/BTNL Cluster

Gene ancestor

PDL1, PDL2 Cluster

CD276 Cluster

BTNL3, BTLN8#
BTN3A1, BTN3A2, BTN3A3#
BTN2A1, BTN2A2, BTN1A1 #
MOG

Butyrophilins

Cluster of rodent SKINT proteins

BTNL2

B7H7 (HHLA2)*
B7H4 (VTCN1)
PDL2 (PDCD1LG2, CD273)
PDL1 (CD274)

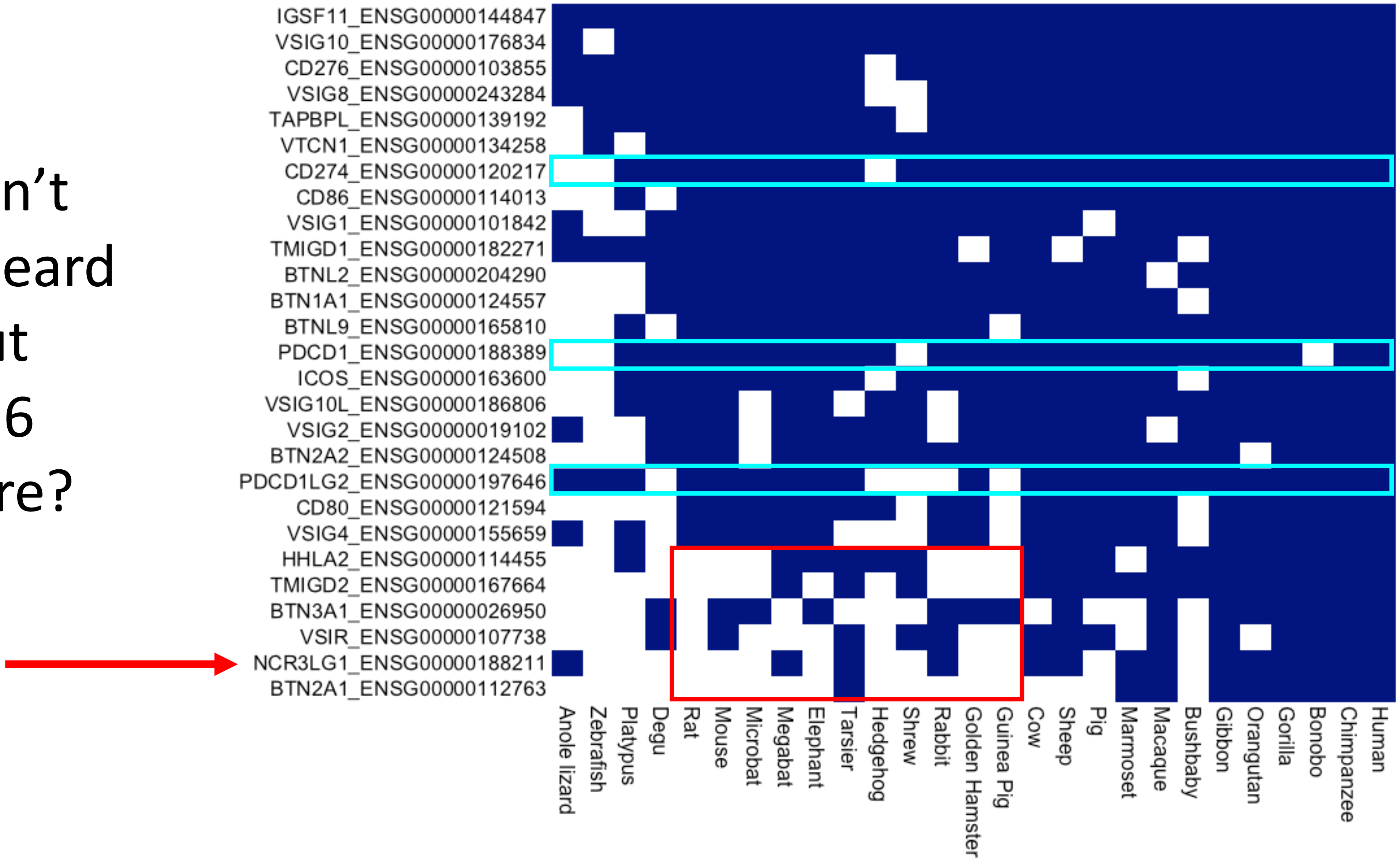
B7H6 (NCR3LG1)*

B7H3 (CD276)

B7.2 (CD86)
B7.1 (CD80)
B7H2 (ICOSLG, CD275)

human
rat
mouse
chicken
fish

Why haven't we heard about B7-H6 before?



PDL1

PD1

PDL2

B7 Genes With no or few Rodentia paralogues

Outgroup (Lizard/Fish/Platypus)

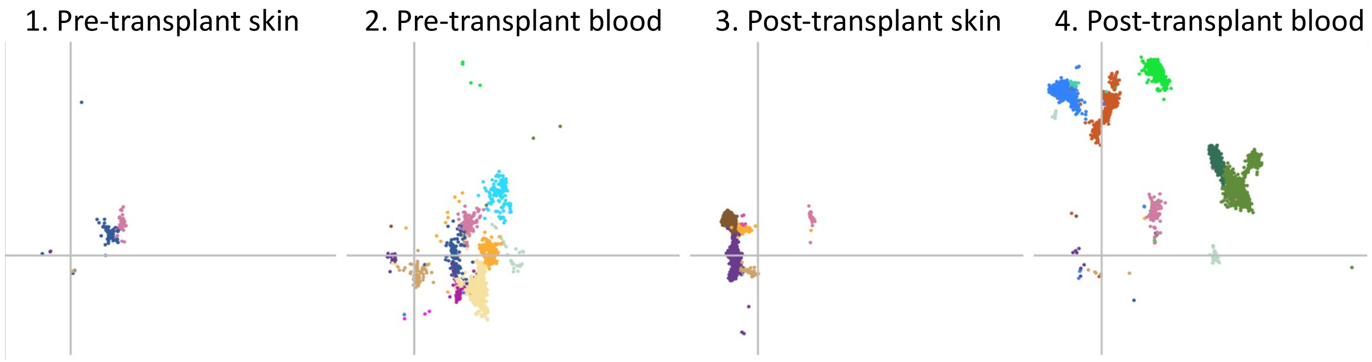
Rodents

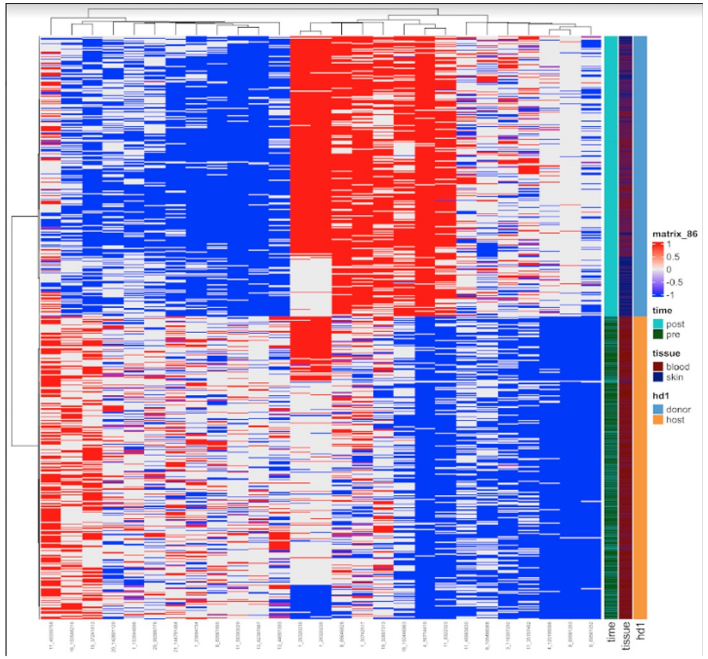
Primates

Unpublished

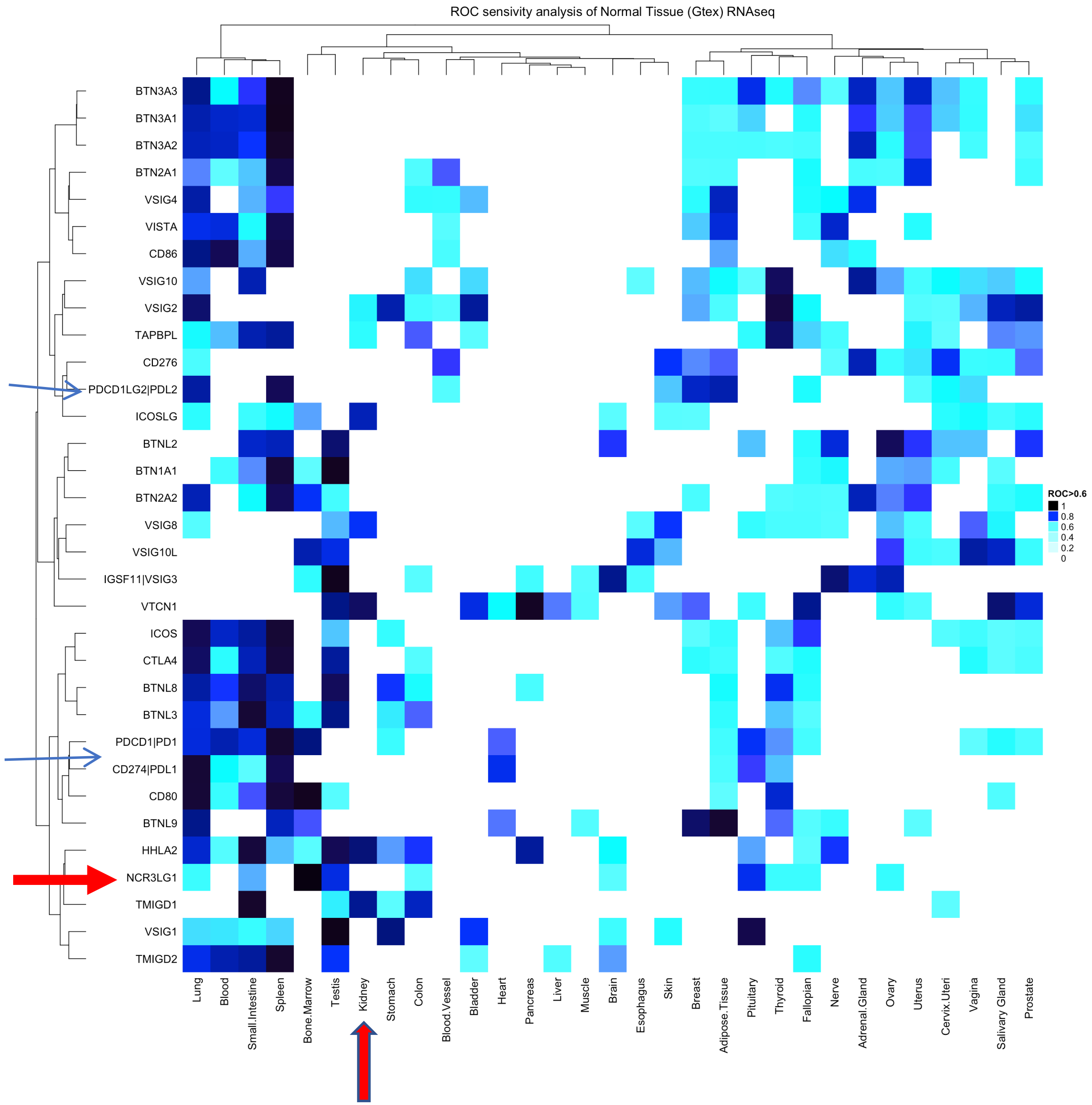
3. Tissue resident immunity and GVHD

- scRNAseq and TCR seq
- Pre/Post transplant
- Blood, Tissue from Receipt and Donor





Tissue Specific of B7 genes


ROC sensivity analysis of Normal Tissue (Gtex) RNAseq

PDL2

PD1

PDL1

B7H6

ROC sensitivity/specificity to identify genes that differentiated different tissues. Most immune genes had high specificity for blood, spleen, small intestine, lung.

Tissue specificity + evolution/GWAS can be used to deliver personalized IO

Unpublished

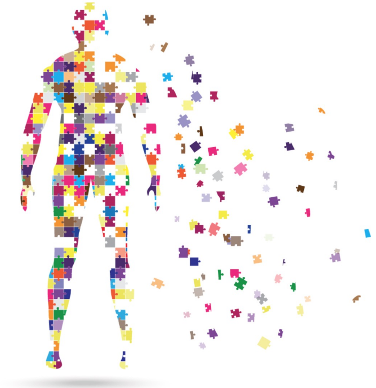
Summary

- Importance of computational oncology and our lab
- Framework for sharing health data for research -eHealth -Hub for Cancer
- Single Cell Genomics and Immuno-Oncology Research
  - CAR T-Cell in renal cancer. Wang et al., Mol Ther Oncolytics 2021
  - Sensitivity to NK cell killing. Scheffer et al., Nat Genet. 2021
  - GVHD and tissue resident cells (unpublished)

Questions

@AedinCulhane

Aedin.Culhane@ul.ie



- Tools and methods to analyse single cell data
  - Corral, Hsu & Culhane, 2021
  - Bioconductor Eckenrode et al, 2021
  - Hackathon Le Cao et al., 2021

- Real-world data (COVID-19 Study-a-thon)

  Roel et al. 2021,

  Lane et al, 2020,

  Burns et al. 2020

- TME immune, stroma cells in cancer

  Wang et al., 2021,

  Dhimolea et al., 2021,

  Sheffer et al., 2021

UNIVERSITY OF LIMERICK
OLLSCOIL LUIMNIGH

Limerick Digital Cancer Research Centre

Dana-Farber Cancer Institute | Department of Data S

HARVARD T.H. CHAN | SCHOOL OF PUBLIC HEALTH

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