Data Science & Precision Medicine

CHEE-ONN LEONG, PHD
Deputy Director of Research, IMU
• 23 pairs of chromosome
• 3.3 billion nucleotide pairs
• 23-30k genes
• Coding ~500k proteins

Genes contain instructions for making proteins

Proteins act alone or in complexes to perform many cellular functions
How long is all your DNA in the body?

\[ 2\text{m} \times (100,000,000,000,000 \text{ cells}) = 2 \times 10^{14}\text{m} \]

Distance from earth to the sun = 150,000,000,000m

\[ 2 \times 10^{14}/1.5 \times 10^{11} = 1,333 \text{ trips} \]

6.6 million rounds trip from Kuala Lumpur to New York
Current Healthcare = Reactive Medicine
What if… we can predict diseases before it manifested?

What if… we can treat diseases based on their molecular mechanism rather than symptoms?

What if… we can tailor treatment based on the biology of individuals?
Gene expression profiling of breast carcinoma distinguish tumor subclasses

Inferior relapse-free and breast cancer-specific survival for patients with basal-like breast cancers

p63 regulates an adhesion programme and cell survival in epithelial cells

Danielle K. Carroll, Jason S. Carroll, Chee-Own Leong, Fang Cheng, Myles Brown, Alex. A. Mills, Joan S. Brugar, and Leif W. Elfsen

p63 is critical for epithelial development yet little is known about the transcriptional programmes it regulates. By characterising transcriptional changes and cellular effects following modulation of p63 expression, we have identified a vital role for p63 in cellular adhesion. Knockdown of p63 expression caused downregulation of cell adhesion-associated genes, cell detachment and anoikis in mammary epithelial cells and keratinocytes. Conversely, overexpression of the TaP63α or cNp63α isoforms of p63 upregulated cell adhesion molecules, increased cellular adhesion and conferred resistance to anoikis. Apoptosis induced by loss of p63 was rescued by signalling downstream of p4 integrin. Our results implicate p63 as a key regulator of cellular adhesion and survival in basal cells of the mammary gland and other stratified epithelial tissues.

p63 mediates survival in squamous cell carcinoma by suppression of p73-dependent apoptosis

James W. Rocco, Chee-Own Leong, Nicolas Kuperwasser, Maurice Philip DeYoung, and Leif W. Elfsen

Summary

We demonstrate that ΔNp63α is an essential survival factor in head and neck squamous cell carcinoma (HNSCC) through its ability to suppress p73-dependent apoptosis. Inhibition of endogenous p63 expression by RNAi induces apoptosis selectively in HNSCC cells that overexpress ΔNp63α. Knockdown of p63 induces the proapoptotic bcl-2 family members Puma and Noxa, and both their induction and subsequent cell death are p53 independent but require transactivating isoforms of p73. Inhibition of p73-dependent transcription by ΔNp63α involves both direct promoter binding and physical interaction with p73. In HNSCC cells lacking endogenous ΔNp63α expression, bcl-2 is instead upregulated and can suppress p73-mediated death. Together, these data define a pathway whereby ΔNp63α promotes survival in squamous epithelial malignancy by repressing a p73-dependent proapoptotic transcriptional program.

Efficacy of Neoadjuvant Ciaplatin in Triple-Negative Breast Cancer

David P. Hrych, Andrea L. Babcock, Amie A. Ruble, Sigrid C. Abdallah, Ignacio A. Negria, Lene Schioler, Cachet Leon, Diana Gallegos, Andrea Benachny, Andy Fairman, Eduard S. Schulze, James P. Moore, Valerie M. Goldschmidt, Alexander Miller, Christopher Ohls, Brian M. Price, Gail R. Miller, and James E. Moore

Abstract

Purpose: Ciaplatin is a chemotherapeutic agent not used routinely for breast cancer treatment. As a DNA intercalating agent, ciaplatin may be effective treatment for harboring TNBC in neoadjuvant breast cancer. Because epidermal growth factor receptor (EGFR) and HER2-overexpressed breast cancer share features suggesting common pathogenesis, we conducted a randomised trial of ciaplatin in TNBC and explored specific biomarkers to identify predictors of response.

Patients and Methods: Twenty-eight women with stage I or II breast cancers lacking estrogen and progesterone receptors (ER/PR−) were treated with ciaplatin for 2 cycles at 3 weeks. All patients had a disease-free interval of at least 1 year postoperatively. Nineteen patients received prior chemotherapy and radiation therapy per their clinican. Clinical and pathologic findings were assessed, and posttreatment tumor samples were evaluated for receptor biomarkers.

Results: Six (22%) of 27 patients achieved pathologic complete responses, including 2 with complete necrosis (CR); 16 (59%) patients had a decrease of ≥75% in the primary tumor volume. Seventy-two percent of patients showed no pathologic responses (Michael S. McShane et al. 2010 for the response rate). Of the 11 patients without a complete or partial remission, 9 of 27 CIAP patients received prior chemotherapy and radiation therapy per their clinican. Fifteen percent of patients experienced gastrointestinal toxicity grade 3/4, and 4 had cardiac toxicity. Patients with a disease-free interval of at least 1 year postoperatively showed a 90% complete response. Additionally, 8 of 27 CIAP patients received prior chemotherapy and radiation therapy per their clinican. A gene expression signature of CIAP6 was found in these patients.

Conclusions: This study provides evidence for the efficacy of neoadjuvant ciaplatin in patients with TNBC. Decreased CIAP6 expression was associated with improved outcomes in patients with TNBC that are cisplatin sensitive. Other biomarkers show promise in predicting ciaplatin response.

The p63/p73 network mediates chemosensitivity to cisplatin in a biologically defined subset of primary breast cancers

Chee-Own Leong, Nick Vlahovic, Maurice Philip DeYoung, Dennis Sigal, and Leif W. Elfsen

Breast cancers lacking estrogen and progesterone receptor expression exhibit distinct gene expression profiles and clinical features, and they comprise the majority of BRCA1-associated tumors. Here we demonstrated that the p63 family member p63 controls a pathway for p73-dependent cisplatin sensitivity specific to these "triolo-negative" tumors. In vivo, ΔNp63α and TaP73α isoforms of p63 are expressed exclusively within a subset of triple-negative primary breast cancers that commonly exhibit mutational inactivation of p53. The p63/p73 network promotes survival of breast cancer cells by binding TaP73α and thereby inhibiting its proapoptotic activity. Consequently, inhibition of p63 by RNA interference led to TaP73α-dependent induction of proapoptotic Bcl-2 family members and apoptosis. Breast cancer cells expressing ΔNp63α and TaP73α exhibited cisplatin sensitivity that was uniquely dependent on TaP73α. Thus, in response to treatment with cisplatin, but not other chemotherapy agents, TaP73α underwent P73-dependent phosphorylation, which prevented the interaction of TaP73α with p53 and induced TaP73α-dependent transcription of proapoptotic Bcl-2 family members and apoptosis. These findings define p63 as a survival factor in a subset of breast cancers; furthermore, they provide what we believe to be a novel mechanism for cisplatin sensitivity in these triple-negative cancers, and they suggest that such cancers may share the cisplatin sensitivity of BRCA1-associated tumors.
Equitable access to technology?
Super-exponential technologies.
Encouraging innovation.

Not 6 decades but 6 years

From $3 billion to $1000

Moore’s “Law”

$5000 2013

$1k 2015


arep.med.harvard.edu/gmc/genome_services.html
Genome vs Genome Analysis

The costs for genome sequencing are falling significantly and the $1000 genome is basically there (you may even get this for free on a collaborative research basis). In parallel, the costs for genome interpretation are increasing. In fact, in the near future, sequencing might not be a big deal anymore – the efforts for interpretation, however, account for most of the required efforts.
Growth of DNA Sequencing

- Recorded growth
- Double every 7 months (Historical growth rate)
- Double every 12 months (Illumina Estimate)
- Double every 18 months (Moore's Law)

Cumulative Number of Human Genomes

Year


1000 Genomes

1st Sanger
IHGSC et al.
Venter et al.

1st 454
Wheeler et al.

1st Illumina
Bentley et al.
Wang et al.
Ley et al.

1st PacBio
Chaisson et al.

Current Capacity
ExAC
TCGA

Worldwide Annual Sequencing Capacity

1 Tbp
1 Pbp
1 Ebp
1 Zbp

# Precision Medicine

**Definition**
Medical approach in which patients are stratified based on their disease subtype, risk, prognosis, or treatment response using specialized diagnostic tests.

**Purpose**
The vision of precision medicine is to provide the right intervention to the right patient, at the right time and dose.

**Personalized medicine**
**Precision medicine**
**Stratified medicine**
**P4 medicine**
The data science and AI hype contrasts with reality

- One might get the impression that enabling personalized medicine is mainly a matter of availability of ‘big data’, sufficient computing power, and modern deep-learning techniques.

- Some authors have even claimed the end of classical, hypothesis-driven science and stated that, in the future, all novel insights would come from an algorithmic analysis of large datasets.
Insufficient prediction performance for clinical practice

Machine learning methods capture and mathematically describe a (complex) signal that is present in a dataset. Their success does not only depend on the number of (patient) samples, but also on the signal-to-noise ratio.

1. The relationships of **patient-specific characteristics** to clinically relevant endpoints are highly complex and non-linear, often varying over time and, typically not well described by one data instance alone.

2. It is challenging to obtain a sufficiently **large patient cohort** with well-defined phenotypes for training and testing models due to cost and time constraints.

3. Clinical outcomes may vary over time and be partially influenced by **factors that are not patient intrinsic** and thus hard to capture (e.g., social and environmental influences).

4. Machine learning models are typically sensitive to **selection biases**, i.e., under- or over-represented specific patient subgroups in the training cohort.
Difficulties in interpretation

Correlation does not imply causation.

1. While machine learning techniques can detect complex patterns in large data and provide accurate predictions, they are unable to provide a deeper theoretical, mechanistic, or causal understanding of an observed phenomenon.

2. Even if an acceptable prediction performance can be achieved, the lack of a clear causal or mechanistic interpretation of machine learning models can hinder acceptance of data science-based solutions by physicians.

3. As researchers collect and analyze increasingly larger sets of data, a greater number of sophisticated algorithms are employed to train predictive models. Some of the computational methods, in particular those based on deep learning techniques, are often criticized for being black boxes.
Insufficient validation from real-world longitudinal data

Longitudinal EMR and claims data have received increasing interest in recent years within the field of personalized medicine since they provide a less biased view on patient trajectories than data from classical clinical trials, which are always subject to certain inclusion and exclusion criteria.

1. The maximal observation horizon in real-world databases is often limited to a certain number of years, some patients are longer observed than others.

2. Data may contain gaps and the exact date of a diagnosis, prescription, or medical procedure cannot be uniquely determined.

3. Classically, validation of a predictive model relies on an appropriate experimental design and randomization. Real-world data often limits the options available for rigorous validation.
Multi-modal patient data

There is an increasing availability of multi-scale, multi-modal longitudinal patient data. The combination of multi-omics with real-world longitudinal data from clinical practice (e.g., EMRs) and mobile health applications marks a further potential for personalized medicine in the future.

1. Different studies are often performed on cohorts of different patients and different experimental approaches are used across studies.

2. Data from different studies becomes difficult to integrate into a joint machine learning model (e.g. different cohorts, different normalization of data across measurement platforms, and different ability to process very large volumes of data in appropriate systems close to or within the clinical infrastructure remains limited).
At present, translation of algorithms for patient stratification into clinical practice is also difficult due to regulatory aspects.

1. Prospective clinical trials required for approval of diagnostic tools by regulatory agencies are very **costly** and the challenges for finding sponsors are high.

2. A commonly stated myth is that health innovation is based on the paradigm of build-and-freeze, which means that software is built, frozen, and then tested in unchanged form for its lifetime. However, development of better stratification algorithms will require a more **seamless updating scheme**.
Data Ownership and Data Sharing

Patient data of any sort, because it is held within medical institutions, appears to belong to that institution. However, these institutions merely act as the custodians of this data - the data is the property of the patient and the access and use of that data outside of the clinical realm requires patient consent.

1. Retrospective hypothesis driven research can be undertaken on specific, anonymized data as with any research, once the study has ended the data should be destroyed.

2. Under the EU General Data Protection Regulation (GDPR), processing of “data concerning health,” “genetic data,” and “biometric data” is prohibited unless one of several conditions applies:
   • Data subject gives “explicit consent”
   • Processing is necessary for the purposes of provision of services or management of health system (etc.)
   • Processing is necessary for reasons of public interest in the area of public health
What is possible today?
<table>
<thead>
<tr>
<th>TREATMENT CATEGORIES</th>
<th>PERCENT OF 2017 APPROVALS</th>
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<tbody>
<tr>
<td>Oncology</td>
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<tr>
<td>Other</td>
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<tr>
<td>Metabolism</td>
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<td>Neurology</td>
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<td>Infectious Diseases</td>
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<tr>
<td>Genetics</td>
<td>5%</td>
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<tr>
<td>Vascular</td>
<td>3%</td>
</tr>
</tbody>
</table>

100% of the 77 Drug and Biologic Treatments for Rare Diseases Approved in 2017
Patient Stratification

The current notion is that NGS-based genomic sequencing will realize “precision medicine”, in which each patient receives individualized therapy based on their genetic alterations in the tumor.

Gene panel testing is a clinically useful approach to investigate the genomic mechanisms related to the therapies.

These include therapy-related signaling pathways, microsatellite instability and a hypermutated phenotype, and deficiency in the DNA double-strand break repair pathways.

NGS-based Panels

Oncomine Dx
Praxis RAS Panel
MSK-IMPACT
FoundationOne CDx
CANCERPLEX
Pattern Recognition

Pattern recognition mainly rely on the prior knowledge with respect to the disease and problem under investigation, quantity, and quality of data, the type of data, and the algorithm itself.

IBM Watson Genomics

Watson for Genomics leveraging AI to extract unstructured data from peer-reviewed literature to continually grow its knowledge base. It provides variant information and clinical content that is up-to-date, based on the latest approved therapeutic options including targeted and immunotherapy options, professional guidelines, biomarker-based clinical trial options, genomic databases and relevant publications.

Apple Watch ECG

Approved by the FDA in September of 2018, the ECG technology on the Apple Watch Series 4 uses electrodes to capture heart rhythm irregularities. This technology is the first consumer-available product that allows users to take an ECG from their own wrist, and can provide critical data to physicians. It can detect atrial fibrillation, a dangerous arrhythmia that can result in stroke if left untreated.
Precision medical imaging has tremendous potential to improve all aspects of the care continuum, thus supporting emerging care approaches that are more targeted, predictive, translational, personalized and effective.

AI-enriched imaging equipment will help adapt and personalize the imaging protocols and procedures while precise radiomic and phenomic datasets from the given clinical context will enable deep learning, thereby reinforcing medical imaging’s contribution to precision medicine.
What could be possible tomorrow?
PRECISION MEDICINE
WHAT TO EXPECT IN THE FUTURE

Increased utility of genomic clinical assays

Targeting hard-to-treat cancers (e.g., GBM, pancreatic cancer)

Functional studies to understand VUS

Liquid biopsy to study drug resistance; early detection

AI for digital pathology, radiology, and systems biology

Platforms

Pan-TCGA

Exome seq
mRNA seq
miRNA seq
Genomic DNA
DNA Meth Array
SNP Array
RPPA

Converged
diverged

Lung adeno
Bladder

Squamous-like
Lung
Head neck
Bladder

BRCA/Luminal
Breast

BRCA/Basal
Breast

BLCA
Bladder

COAD/READ
Colon
Rectum

Same tissue origin

OV
Ovary

UCEC
Endometrium

KIRC
Kidney

GBM
Glioblastoma

Myelogenous leukemia

Graphic based on conversation with Elaine Mardis, PhD; Courtesy of the American Association for Cancer Research.

Cell 2014 158, 929-944 DOI: (10.1016/j.cell.2014.06.049)
Identification of inhibitors synergizing gemcitabine sensitivity in the squamous subtype of pancreatic ductal adenocarcinoma (PDAC)

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<td>MTOR inhibitor</td>
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\[ P = 0.0302 \]

Median survival: 30.0 vs 23.7 vs 25.6 vs 13.3 months

n = 98
Association of BRCA1- and BRCA2-deficiency with mutation burden, expression of PD-L1/PD-1, immune infiltrates, and T cell-inflamed signature in breast cancer

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Abstract

Immune checkpoint inhibitors have demonstrated effective anti-tumour response in cancer types with high mutation burden (e.g. melanoma) and in subset of cancers with features of genomic instability (e.g. mismatch-repair deficiency). One possible explanation for this effect is the increased expression of immune checkpoint molecules and pre-existing adaptive immune response in these cancers. Given that BRCA1 and BRCA2 are integral in maintaining genomic integrity, we hypothesise that the inactivation of these genes may give rise to breast cancers with such immunogenic phenotype. Therefore, using two large series of publicly available breast cancer datasets, namely that from The Cancer Genome Atlas and Wellcome Trust Institute, we sought to investigate the association between BRCA1- and BRCA2-deficiency with features of genomic instability, expression of PD-L1 and PD-1, landscape of inferred tumour-infiltrating immune cells, and T-cell-inflamed signature in breast cancers. Here, we report that BRCA1- and BRCA2-deficient breast cancers were associated with features of genomic instability including increased mutation burden. Interestingly, BRCA1- but not BRCA2-deficient breast cancers were associated with increased expression of PD-L1 and PD-1, higher abundance of tumour-infiltrating immune cells, and enrichment of T-cell-inflamed signature. The differences in immunophenotype between BRCA1- and BRCA2-deficient breast cancers can be attributed, in part, to PTEN gene mutation. Therefore, features of genomic instability such as that mediated by BRCA1- and BRCA2-deficiency in breast cancer were necessary, but not always sufficient, for yielding T-cell-inflamed tumour microenvironment, and by extension, predicting clinical benefit from immunotherapy.

Association between BRCA status and T cell-inflamed signature in relation to PTEN mutation status. (A) PTEN protein expression stratified by PTEN copy number alteration and point mutation. (B) Proportion of PTEN mutant samples stratified by BRCA status. (C-E) tSNE visualisation of BRCA1- and BRCA2-deficient breast cancers. Colour represents T cell-inflamed signature score divided at the median, PTEN mutation status, and BRCA status, respectively. (F-G) Distribution of T cell-inflamed signature scores in BRCA-proficient and BRCA1-deficient breast cancers with and without PTEN mutation. n.s.: Not statistically significant, ** p < 0.01.
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Medical Research Council

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