Cancer: A Computational Disease That AI Can Cure

Robert Engelmore Memorial Lecture

Jay M. Tenenbaum
CEO and Chief Scientist
CollabRx
<table>
<thead>
<tr>
<th>KSL Legacy in AI and Biomedicine</th>
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<tbody>
<tr>
<td>Russ Altman</td>
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<tr>
<td>Bruce Buchanan</td>
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<td>Ed Feigenbaum</td>
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<td>Peter Friedland</td>
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<td>Peggy Karp</td>
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<td>Josh Lederberg</td>
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<td>Mark Musen</td>
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<td>Tom Rindfleisch</td>
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<td>Ted Shortliffe</td>
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<td>Mark Stefik</td>
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| Blackboard systems             |
| Rule-based systems             |
| Probabilistic methods          |
| Molgen                          |
| Mycin                           |
| Oncocin                         |
| PharmGKB                        |
| Protege                         |
| Stanford Medical Informatics Lab |
| Center for Biomedical Informatics Research |
Outline

• Cancer – The Forty Years’ War
• A new “N-of-1” paradigm
  - CollabRx ONE
  - Cancer Commons
• AI opportunities and challenges
The Forty Years’ War

Age-adjusted death rates per 100,000 standard population  
Source: NY Times
Median Survival
Metastatic Melanoma

Drug Discovery
Trials Phase 1
Trials Phase 2
Trials Phase 3
FDA Approval

Year
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Time’s Up
Medical Guesswork
From heart surgery to prostate care, the medical industry knows little about which treatments really work

BY JOHN CAREY (P. 72)
The Problem
LOS ANGELES, April 6 - A cancer treatment that has been under development for more than 40 years failed in the first clinical trial in which it was compared with a placebo. The failure, announced Wednesday, was a blow to the field of so-called cancer vaccines and to the two companies developing the treatment, Serono and CancerVax.
The Trouble With Trials

- Based on population statistics vs. individual response
- Results may not apply to a given individual
- Accepts marginal drugs and rejects good ones
- Goal of testing a drug raises ethical issues and minimizes learning
Cancer In The Genomics Age

- **c-KIT** - Imatinib mesylate
- **NRAS**
  - 60% mutated
  - 10-20% amplified
- **PI3K**
- **PTEN**
- **mTOR**
- **AKT**
  - 20% mutated
  - 15-50% deleted/mutated/silenced
- **Bcl-2, Bcl-xL, Mcl-1**
- **Bcl-xL**
- **BAX**
- **NOXA, PUMA**
- **BIM, BID, BAD**
- **p53**
  - 10% mutated
- **CDKN2A**
  - 30-70% deleted/mutated/silenced
- **CDK4/6**
- **p16**
- **Cyclin D**
- **p14ARF**
- **MDM2**

**Other Elements:**
- **G1/S progression**
- **DNA damage, cellular stresses**
- **Apoptosis, chemosensitivity**
- **Growth, metastasis**
Outline

• Cancer – The Forty Years’ War
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• AI opportunities and challenges
The Opportunity

Use genomics, computational / systems biology and the Internet to:

• **Integrate** the worlds of cancer care and research

• **Personalize treatments** based on the most up to date data and knowledge

• **Aggregate the learnings** to rapidly improve the standard of care
15 Years To 3 Months

Year 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Drug Discovery

Trials Phase 1
Trials Phase 2
Trials Phase 3

FDA Approval
Replace Large Trials With...

Drug Discovery
Trials Phase 1
Trials Phase 2
Trials Phase 3
FDA Approval

Year 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
An N-of-1 Trial

Year 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Drug Discovery  Causal Modeling  FDA Approval
Replace Discovery With…

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Drug Discovery

FDA Approval
All Approved + Investigational Drugs

Year 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

Drug Discovery

FDA Approval
Years To Months

Month 1 1.5 2 2.5 3

Computational Biology
Years To Months

Month 1 1.5 2 2.5 3

Computational Biology
Drive Discovery By Aggregation
Therapies For Sub-Types

Month
1 1.5 2 2.5 3

Computational Biology
Emerging Model Of Therapy Identification (lung)

EGFR mutation?

KRAS mutation?

Tarceva

++

?
Outline

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  - CollabRx ONE
  - Cancer Commons
• AI opportunities and challenges
CollabRx ONE
Melanoma Reference Model

Figure FROM: J Invest Dermatol. 2008 Nov;128(11):2575-95.
Melanoma genetics and therapeutic approaches in the 21st century: moving from the benchside to the bedside.
Hocker TL, Singh MK, Tsao H.
Outline

• Cancer – The Forty Years’ War
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  - Cancer Commons
• AI opportunities and challenges
Cancer Commons: Rapid Learning Community

Biologists
Clinical Researchers
Physicians
Patients

CollabRx Platform

Specimens
Genomics
in silico
in vitro
in vivo
in patient

Reference Models
CollabRx ONE Application

- Validation Studies
- Patient
- Oncologist
- Hospital
- Translational Biocomputing
- Molecular Analytics
Melanoma Research Alliance

CollabRx Platform

Reference Model

Drug and RNAi Screens

Trials

Community Oncology

Genome

Transcriptome

Specimen Bank

DANA-FARBER CANCER INSTITUTE

BROAD INSTITUTE

JOHN WAYNE CANCER INSTITUTE at Saint John’s Health Center

MASS GENERAL

Penn University of Pennsylvania
Outline

- Cancer – The Forty Years’ War
- A new “N-of-1” paradigm
  - CollabRx ONE
  - Cancer Commons
- AI opportunities and challenges
Thousands of adaptively-planned individual treatment experiments
Integrate the resulting evidence to infer the causal mechanisms of tumors and drugs
Generalization

Apply the resulting knowledge to new cases
Search

Reference Models

FIGURE 4A
CollabRx ONE Knowledge Levels

Omics
Pathway Analysis
Mechanism Analysis
Target Identification
Treatment Planning

The Cancer Genome Atlas
Gene Expression Omnibus
Pathway Commons
INGENIETY®
KEGG
PubMed.gov
DrugBank
ClinicalTrials.gov
Hierarchical Bayesian Learning
AI Opportunities

- Knowledge management
- Hierarchical planning
- Learning and generalization
Connecting the Dots

Growth factors and tyrosine protein kinases in normal and malignant melanocytes.

Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor.

Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ.
Division of Hematology and Medical Oncology, Department of Medicine, Oregon Health Sciences University, Portland, OR.

STI 571 is a small-molecule tyrosine kinase inhibitor that selectively inhibits c-kit activity.

STI 571 (formerly SU 11248) is a potent inhibitor of c-kit tyrosine kinase activity. The IC50 for c-kit inhibition by STI 571 in the Molt-4 cell line is approximately 100 nM. STI 571 also inhibits the tyrosine kinase activity of the wild-type c-kit receptor.

Potential use of imatinib mesylate in ocular melanoma and liposarcoma expressing immunohistochemical c-KIT (CD117)

KIT is a transmembrane tyrosine kinase receptor in which the extracellular portion binds a ligand known as stem-cell factor and the intracellular portion contains the kinase enzymatic domain. KIT is similar in structure to several other receptor tyrosine kinases with oncogenic capabilities, including platelet-derived growth factor receptors (PDGFR) A and B.

KIT inhibition by STI 571 results in the downregulation of the KIT receptor.

"These findings show that STI 571 inhibits c-kit..." (2000)

"We determined c-kit expression. We decided to treat these patients with palliative imatinib mesylate, a tyrosine kinase inhibitor of KIT and PDGF-R." (2003)
1991: The uncontrolled growth of melanomas is due, in part, to constitutive activation of receptors with tyrosine kinase activity, esp. c-kit.

2000: Gleevec selectively inhibits c-kit.

2003: We determined c-kit expression and so decided to treat with palliative Gleevec, a tyrosine kinase inhibitor of KIT.
Smart Search and Analysis of ASCO Abstracts: The 2003 ASCO Pilot Breast Cancer Information Exchange (BCIE) project

A.T. Rappaport, D.R. Adamson, L. Shih, R. G. Smith, M. Tenenbaum, B. Khoo, S. Cho, A.C. Wolff, R.W. Carlson, and D. Whippen; Medstory, Inc., Burlingame, CA; ASCO, Alexandria, VA; Stanford University, Palo Alto, CA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Providing powerful, targeted and precise access to ASCO information
Results

- 95% of authors voluntarily populated the reference model.
- >70% of users retrieved abstracts via the model.
Locally Advanced
Very high: T3b-T4

RT (3D-CRT/IMRT with IGRT) + short-term neoadjuvant/concomitant/adjuvant ADT (4-6 mo) h
or Long-term ADT (2-3 y) h
or Radical prostatectomy (selected patients: low volume, no fixation + pelvic lymph node dissection)

Positive margins:
• Observation
• RT h
• ADT h
• Active surveillance

Lymph node metastasis:
• Undetectable PSA
• Detectable PSA

See Surveillance (PROS-4)
See Surveillance (PROS-4)
See Salvage Therapy (PROS-5)
MATCHING TRIALS

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<th>Physician</th>
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<tr>
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<tr>
<td>Date of Birth:</td>
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<tr>
<td>Dr. Smith</td>
<td>123-456-7890</td>
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**Clinical Trials**

**Chemotherapy Followed by Infusion of DMF6 Cells to Treat Metastatic Melanoma**
- **Conditions:** Melanoma; Malignant Melanoma; Melanoma, Experimental
- **Interventions:** Drug: DMF5 Melanoma Reactive TIL; Drug: Cyclophosphamide; Drug Fludarabine

**Gene Tests and Status**

<table>
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<tr>
<th>Gene Test</th>
<th>Status</th>
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**Advertisements**

- Add cases
- View related cases
- Confidentially discuss this case with a professional trial counselor

Powered by CollabRx®
Knowledge Challenge

To organize the world’s knowledge of cancer biology and therapeutics

and

Make it *actionable* for researchers and clinicians
Planning

- Combination therapies
- Specimens, $, drug access
- Constraints, ethics, alignment of incentives
- Diseases and patients
The Search For Cures
Succeed Slowly
Fail Fast
Fail Fast
Bed to Bench

5 yrs  3 yrs  1 yr

X  X  X
Planning Challenge

Adaptively plan individual treatment protocols to achieve optimal outcomes while maximizing the learnings for other patients and cancer research.
Learning

for matching and trials

tumors and drugs
Learning

Reference Models

Figure 4A
CollabRx ONE Knowledge Levels

Omics
Pathway Analysis
Mechanism Analysis
Target Identification
Treatment Planning

The Cancer Genome Atlas
Gene Expression Omnibus
Pathway Commons
INGENIUTY
KEGG
PubMed.gov
DrugBank
ClinicalTrials.gov
Learning Challenge

- Integrate the genomic and response data from individual treatment experiments
- Infer the true causal mechanisms of tumors and drugs
- Generalize the resulting knowledge so that it can be applied to new cases.
Summary

• Cancer – The Forty Years’ War
• A new “N-of-1” paradigm
  - CollabRx ONE
  - Cancer Commons
• AI opportunities and challenges
Grand Challenge: Beat Cancer

- Organize the world’s knowledge of cancer biology and therapeutics
- Adaptively plan thousands of ethical treatment “experiments”
- Integrate the resulting data to infer the true causal mechanisms of tumors and drugs
- Generalize the resulting knowledge so that it can be applied to new cases.
Thank You

jmt@collabrx.com