Translational Research

Overview
The Division of Translational Research at BIDMC provides a unique "home" for faculty who play a major role in the infrastructure for clinical/translational investigation. At its inception, the division was integrated with the Harvard-Thorndike General Clinical Research Center (GCRC) of the Beth Israel Deaconess Medical Center. Recently, the GCRC was incorporated into the Harvard Clinical Translational Science Center (CTSC) funded through the NIH Clinical and Community Research Centers Program.
From Bench to Bed & Back to Bench

Ahmad Samir. MBBCh (MD), MSc
For the 1854 cholera outbreak in London's Broad Street region, John Snow created this map, first shown on December 4, 1854 at a meeting of the London Epidemiological Society, which was later published in his book, On the Mode of Communication of Cholera, 2nd Edition. Snow used bars to represent deaths that occurred at the specified households.

Source: http://www.ph.ucla.edu/EPI/snow/snowmap1_1854_lge.htm
Detailed section of Snow’s 1854 map (pumps shown highlighted)

Source: http://www.ph.ucla.edu/EPI/snow/snowmap1_1854_lge.htm
Section of map submitted by John Snow to the Cholera Inquiry Committee of St. James Parish, later issued as part of the Committee's general report in July 1855. Snow used bars to represent deaths that occurred at the specified households.

Source: http://www.ph.ucla.edu/EPI/snow/mapsbroadstreet.html
The distinction between these 2 definitions of translational research was articulated by the Institute of Medicine’s Clinical Research Roundtable,⁵ which described 2 “translational blocks” in the clinical research enterprise and which some now label as T1 and T2. The first roadblock (T1) was described by the roundtable as “the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans.” The roundtable described the second roadblock (T2) as “the translation of results from clinical studies into everyday clinical practice and health decision making.”
Funding

• $22.1 billion NIH budget for 2002 included
• $9.1 billion for “applied and development research” ($13.0 billion for basic research)
• but only $787 million for health services research.
Definition

Translational research, “transforms scientific discoveries arising from the laboratory, clinical, or population studies into clinical applications...”

Source: National Cancer Institute, National Institutes of Health
Two Way Street
Source: National Cancer Institute
Two phase
The current National Institutes of Health (NIH) Roadmap for Medical Research includes 2 major research laboratories (bench and bedside) and 2 translational steps (T1 and T2). Historically, moving new medical discoveries into clinical practice (T2) has been haphazard, occurring largely through continuing medical education programs, pharmaceutical detailing, and guideline development. Proposed expansion of the NIH Roadmap (blue) includes an additional research laboratory (Practice-based Research) and translational step (T3) to improve incorporation of research discoveries into day-to-day clinical care. The research roadmap is a continuum, with overlap between sites of research and translational steps. The figure includes examples of the types of research common in each research laboratory and translational step. This map is not exhaustive; other important types of research that might be included are community-based participatory research, public health research, and health policy analysis.
Three phase

T indicates translation. T1, T2, and T3 represent the 3 major translational steps in the proposed framework to transform the health care system. The activities in each translational step test the discoveries of prior research activities in progressively broader settings to advance discoveries originating in basic science research through clinical research and eventually to widespread implementation through transformation of health care delivery. Double-headed arrows represent the essential need for feedback loops between and across the parts of the transformation framework.
Four phase

T1: From Gene Discovery to Health Application
T2: From Health Application to Evidence-Based Guideline
T3: From Guideline to Health Practice
T4: From Health Practice to Impact

HuGE

Guideline Development
Implementation Dissemination Diffusion Research
Outcomes Research

ACCE

Phase I Trials
Phase II Trials
Phase III Trials
Phase IV Trials
The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention?

Muin J. Khoury, MD, PhD, Marta Gwinn, MD, MPH, Paula W. Yoon, PhD, MPH, Nicole Dowling, PhD, Cynthia A. Moore, MD, PhD, and Linda Bradley, PhD
Goal: Human Health Improvements

- **T0** Identify problems, opportunities and approaches
- **T1** Discovery or foundational research
- **T2** Health application to assess efficacy
- **T3** Health practice; science of dissemination and implementation
- **T4** Evaluation of health impact on real world populations
# The Translation Continuum

<table>
<thead>
<tr>
<th>Basic Scientific Discovery</th>
<th>Early Translation</th>
<th>Late Translation</th>
<th>Dissemination</th>
<th>Adoption</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Promising gene</td>
<td>• Partnerships</td>
<td>• Phase III trials</td>
<td>• To community providers</td>
<td>• Adoption of advance by providers, patients, and public</td>
</tr>
<tr>
<td>• Basic epidemiological finding</td>
<td>• Intervention development</td>
<td>• Regulatory approval</td>
<td>• To patients and public</td>
<td>• Payment mechanisms to enable adoption</td>
</tr>
<tr>
<td>• Basic epidemiological finding</td>
<td>• Health services research to support dissemination and adoption</td>
<td>• Partnerships</td>
<td>• Partnerships</td>
<td>• Partnerships</td>
</tr>
</tbody>
</table>

- **Basic Scientific Discovery**
- **Early Translation**
- **Late Translation**
- **Dissemination**
- **Adoption**
<table>
<thead>
<tr>
<th>Research Phase</th>
<th>Definition</th>
<th>Type of Research</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₀</td>
<td>Identification of opportunities and approaches to health problem.</td>
<td>Basic research question</td>
<td>Are there specific gene mutations associated with breast cancer?</td>
</tr>
<tr>
<td>T₁</td>
<td>Discovery of candidate health application</td>
<td>Phase I and II clinical trials; observational studies</td>
<td>Is there an association between BRCA mutations and breast cancer?</td>
</tr>
<tr>
<td>T₂</td>
<td>Health application to evidence-based practice guidelines</td>
<td>Phase III clinical trials; observational studies; evidence synthesis and guidelines development</td>
<td>What is the positive predictive value of BRCA mutations in at-risk women?</td>
</tr>
<tr>
<td>T₃</td>
<td>Practice guidelines to health practices</td>
<td>Dissemination research; implementation research; diffusion research Phase IV clinical trials</td>
<td>What proportion of women who meet the family history criteria are tested for BRCA and what are the barriers to testing?</td>
</tr>
<tr>
<td>T₄</td>
<td>Practice to population health impact</td>
<td>Outcomes research (includes many disciplines); population monitoring of morbidity, mortality, benefits, and risks studies</td>
<td>Does BRCA testing in asymptomatic women reduce breast cancer incidence or improve outcomes?</td>
</tr>
</tbody>
</table>
Is Translational Research New?

Example: 1854 Cholera epidemic in London

Identification of Broad Street pump required

- Forgoing the existing theory of miasma
- Creating an alternative theory
- Compiling data from more than one source
- In-depth knowledge of the environment
- Understanding of human behavior
- Ability to communicate and display the findings
- Risk taking and innovation

http://www.makingthemodernworld.org.uk/learning_modules/geography/05.TU.01/?section=2
How much time does it take
How much successful?
Trials are per indication

<table>
<thead>
<tr>
<th>Drug (Target)</th>
<th>Indication</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Status / Anticipated Milestones</th>
<th>Rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trafect-EN (CCR9)</td>
<td>Crohn’s Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Three Phase III clinical trials ongoing</td>
<td>GSK (exercised option in Dec. 2009)</td>
</tr>
<tr>
<td>CCXI40 (CCR2)</td>
<td>Diabetic Nephropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase II complete in type 2 diabetics, Two Phase II clinical trials ongoing, trials complete by end of 2012</td>
<td>ChemoCentryx</td>
</tr>
<tr>
<td>CCX354 (CCR1)</td>
<td>Rheumatoid Arthritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase II proof-of-concept (POC) trial complete</td>
<td>GSK (exercised option in Nov. 2011)</td>
</tr>
<tr>
<td>CCXI68 (C5aR)</td>
<td>Vasculitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase II POC trial ongoing, trial complete by end of 2012</td>
<td>GSK option following successful POC trial</td>
</tr>
<tr>
<td>CCX832 (ChemR23)</td>
<td>Skin Inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase I complete</td>
<td>GSK option following successful POC trial</td>
</tr>
<tr>
<td>CCX662 (CXCR7)</td>
<td>Glioblastoma Multiforme</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preclinical, Initiate Phase I in second half of 2012</td>
<td>ChemoCentryx</td>
</tr>
<tr>
<td>(CCR4)</td>
<td>Atopic Dermatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preclinical</td>
<td>ChemoCentryx</td>
</tr>
<tr>
<td>(CCR9) Next-Gen</td>
<td>Ulcerative Colitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preclinical</td>
<td>ChemoCentryx</td>
</tr>
<tr>
<td>(CXCR6)</td>
<td>Chronic Hepatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preclinical</td>
<td>ChemoCentryx</td>
</tr>
<tr>
<td>(CCR6)</td>
<td>Autoimmune Diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Preclinical</td>
<td>ChemoCentryx</td>
</tr>
</tbody>
</table>

Source: http://www.sec.gov/Archives/edgar/data/1340652/000119312512020446/d237820ds1a.htm
Knowledge in Biology
Hallmarks of Cancer: The Next Generation

Douglas Hanahan\textsuperscript{1,2,*} and Robert A. Weinberg\textsuperscript{3,*}
Figure 6. Therapeutic Targeting of the Hallmarks of Cancer
Gleevec

CML
>> hyperactive bcr-abl protein; abnormal tyrosine kinase
Lugo et al., 1990
>> ST1571
phase I trial; 31 patients. all 31 >>
complete remission & some cytogenetic remission
>> Imatinib / Gleevec
Miracle

Survival in newly diagnosed CP-CML by year of therapy.

• Single target
Other stories

• EGFR
• HER 2

• ➔ Targeted therapy ➔ Personalized medicine
Translational research in oncology: key bottlenecks and new paradigms

Accession information: doi:10.1017/S1462399410001638; Vol. 12; e32; October 2010

Richard Simon
<table>
<thead>
<tr>
<th>Year</th>
<th>Indication</th>
<th>Drug</th>
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</thead>
<tbody>
<tr>
<td>2009</td>
<td>Renal cell carcinoma</td>
<td>Everolimus, bevacizumab, pazopanib</td>
</tr>
<tr>
<td></td>
<td>Chronic lymphocytic leukaemia</td>
<td>Ofatumumab</td>
</tr>
<tr>
<td></td>
<td>Cervical cancer prevention</td>
<td>Cervarix</td>
</tr>
<tr>
<td></td>
<td>T cell lymphoma</td>
<td>Prolastaxate, romidepsin</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>Fentanyl buccal</td>
</tr>
<tr>
<td></td>
<td>Uric acid management</td>
<td>Rasburicase</td>
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<tr>
<td>2008</td>
<td>Prostate cancer</td>
<td>Degarelix</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma</td>
<td>Levoleucovorin</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin lymphoma</td>
<td>Plerixafor, bendamustine hydrochloride</td>
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<tr>
<td></td>
<td>Nausea and vomiting</td>
<td>Granisetron</td>
</tr>
<tr>
<td>2007</td>
<td>Breast cancer prevention</td>
<td>Raloxifene</td>
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<tr>
<td></td>
<td>Breast cancer</td>
<td>Ixabepilone, lapatinib</td>
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<tr>
<td></td>
<td>Small-cell lung cancer</td>
<td>Topotecan</td>
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<tr>
<td></td>
<td>Chronic myeloid leukaemia</td>
<td>Nilotinib</td>
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<td></td>
<td>Renal cell carcinoma</td>
<td>Temsirolimus</td>
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<td>2006</td>
<td>Cervical cancer prevention</td>
<td>Gardasil</td>
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<td>Colorectal cancer</td>
<td>Panitumumab</td>
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<td></td>
<td>Chronic myeloid leukaemia</td>
<td>Dasatinib</td>
</tr>
<tr>
<td></td>
<td>Renal cell carcinoma, gastrointestinal stromal tumour</td>
<td>Sunitinib</td>
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<td>2005</td>
<td>Renal cell carcinoma</td>
<td>Sorafenib</td>
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<td></td>
<td>T cell leukaemia/lymphoma</td>
<td>Nelarabine</td>
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<td>2004</td>
<td>Colorectal cancer</td>
<td>Cetuximab, bevacizumab</td>
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<td>Erlotinib</td>
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<tr>
<td></td>
<td>Mesothelioma</td>
<td>Pemetrexed</td>
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<td></td>
<td>Paediatric acute lymphoblastic leukaemia</td>
<td>Clofarabine</td>
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<tr>
<td></td>
<td>Hypercalcaemia</td>
<td>Cinacalcet</td>
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<td>2003</td>
<td>Non-small-cell lung cancer</td>
<td>Gefitinib</td>
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<tr>
<td></td>
<td>Prostate cancer</td>
<td>Abarelix</td>
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<td></td>
<td>Benign prostatic hyperplasia</td>
<td>Alfuzosin</td>
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<tr>
<td></td>
<td>Multiple myeloma</td>
<td>Bortezomib</td>
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<td></td>
<td>Non-Hodgkin lymphoma</td>
<td>Corixa</td>
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<tr>
<td></td>
<td>Nausea and vomiting</td>
<td>Palonosetron, aprepitant</td>
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<td></td>
<td>Osteoporosis prevention</td>
<td>Premarin</td>
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<td>2002</td>
<td>Prostate cancer</td>
<td>Leuprolide</td>
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<td>Colorectal cancer</td>
<td>Oxaliplatin</td>
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<td></td>
<td>Breast cancer</td>
<td>Fulvestrant</td>
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<tr>
<td></td>
<td>Gastrointestinal stromal tumour</td>
<td>Imatinib</td>
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<td></td>
<td>Non-Hodgkin lymphoma</td>
<td>Ibritumomab</td>
</tr>
<tr>
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<td>Multiple myeloma</td>
<td>Zoledronic acid</td>
</tr>
<tr>
<td></td>
<td>Haematological support</td>
<td>Neulasta</td>
</tr>
<tr>
<td></td>
<td>Pancreatic dysfunction</td>
<td>Secretin</td>
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</table>
Box 1. Barriers to effective translational research

1. Complexity of research with human subjects
   Regulatory issues, human subject protection, intellectual property issues, lack of funding, fragmented infrastructure, shortage of trained investigators and shortage of resources for including sufficient patients

2. Goal-oriented, high-risk, team research is difficult to sustain in academic settings

3. Lack of focus on key high-risk translational barriers and opportunities

4. Limitation in understanding oncogenesis and lack of identification of key molecular targets

5. Need for new clinical trial designs appropriate for predictive personalised medicine
Using markers for choosing Treatment

Use of theragnostic markers to select drugs for phase II/III trials for Alzheimer disease
Henrik Zetterberg*, Niklas Mattsson, Kaj Blennow and Bob Ossen

Abstract
In a slowly progressive disorder like Alzheimer disease, evaluation of the clinical effect of novel drug candidates requires large numbers of patients and extended treatment periods. Current cell- and animal-based disease models of Alzheimer disease are poor at predicting a positive treatment response in patients. To help bridge the gap between disease models and large and costly clinical trials with high failure rates, biomarkers for the intended biochemical drug effect may be of value. Such biomarkers may be called ‘theragnostic’. Here, we review the literature addressing the prospective value of these biomarkers.

Background
Three decades of multidisciplinary research have resulted in detailed knowledge of the molecular pathogenesis of Alzheimer disease (AD) [1]. We know that the symptoms of AD are caused by synaptic dysfunction and neuronal death in the areas of the brain that are involved in memory consolidation and other cognitive functions [1]. This neurodegeneration is firmly associated with aggregation of the 40- to 42-amino acid amyloid beta (Aβ) peptide into senile plaques, phosphorylation and aggregation of tau proteins that form neurofibrillary tangles, and microglial activation that may be a protective response or contribute to the neuronal dysfunction and damage [2]. The relative importance of these processes to the clinical presentation of the disease remains uncertain.

Clinical trials of novel anti-AD drugs face at least two major challenges. First, the new types of drug candidates that attack basic disease processes are likely to be most effective in early stages of the disease, before neuronal degeneration has become too widespread and severe [3]. However, clinical methods that recognize early AD are lacking. Second, the drug candidates may slow down the degenerative process without having any immediate and easily recognizable symptomatic effect [4]. This makes evaluation of the drug effect difficult. Theragnostic biomarkers (that is, biomarkers that detect and monitor biochemical effects of the drug) may help solve some of these problems. Here, we review three pathological processes that are thought to be involved in the complex surge of AD – namely the amyloid cascade, abnormal tau phosphorylation, and microglial activation with neuroinflammation – and the currently available biomarkers thought to reflect them (Figure 1).

Core biomarkers of Alzheimer disease
It is well established that cerebrospinal fluid (CSF) levels of total tau (T-tau), phospho-tau (P-tau), and the 42-amino acid fragment of Aβ (Aβ42) reflect core elements of the AD process [3]. T-tau is a marker of cortical axonal degeneration and disease activity [5-7]. P-tau reflects neurofibrillar pathology [8,9]. Aβ42 is a marker of plaque pathology [9-12]. Together, these biomarkers identify AD and predict AD in mild cognitive impairment (MCI) with a sensitivity and specificity of 75% to 95% [3]. The predictive power is, however, suboptimal in general populations as compared with MCI cohorts because of the lower prevalence of incipient AD in this group [13]. Plasma biomarkers reflective of pathophysiological changes in the AD brain are highly warranted, the subject of intense research, but unfortunately still lacking [3].

Drug targets
Amyloid
Experimental data, as well as longitudinal studies in humans, suggest that certain forms of Aβ may act as initiators in the disease process with potent toxic effects at the synaptic level [2]. Based on this knowledge, novel treatments aimed at inhibiting Aβ toxicity have been developed and are being tested in patients [14]. These include secretase inhibitors and modulators that affect the production of Aβ from amyloid precursor protein (APP), immunotherapy aimed at increasing the clearance...
Biomarkers and new clinical trial designs for predictive personalised medicine

a Targeted/enrichment design
Evaluate test
- Test-positive Randomise (Treatment T)
- Test-negative Off study (Treatment C)

b Stratification design
Evaluate test
- Test-positive or -negative Randomise (Treatment T)
  - Treatment C

Marker strategy design
Randomise
- Perform test and employ test-determined treatment
- Standard of care treatment

Three designs for prospective clinical trials of predictive biomarker classifiers
Creation of a new intellectual discipline

• **Strengths**
  – Designed to improve health
  – Systems based approach proposed
  – Multi-disciplinary
  – Innovative
  – Flexible and responsive to environment
  – Collaborations within and outside of academic centers
Diffusion of Innovations in Service Organizations: Systematic Review and Recommendations

TRISHA GREENHALGH, GLENN ROBERT, FRASER MACFARLANE*, PAUL BATE, and OLIVIA KYRIAKIDOU*

The Milbank Quarterly, Vol. 82, No. 4, 2004 (pp. 581–629) © 2004 Milbank Memorial Fund. Published by Blackwell Publishing.
How physicians find themselves

Translational Research

• Dissemination of the innovation

• Adoption of the innovation

• Maintaining the innovation

• Refining and evolving as body of knowledge expands
Dissemination

• How to disseminate findings into practice?

  – Theory based interventions
    • Evidence based interventions
    • Diffusion of innovation
  – Guidelines
    • www.guidelines.gov
  – Regulation
Adoption

• Organizations
  – Systems change theories

• Individuals
  – Behavioral change theories
    • Health Belief Model
    • Theory of Reasoned Action/Planned Change
    • Social Cognitive Theory
    • Stages of change
Maintenance

• Adherence theories
  – Short term adherence theories
  – Long term adherence theories
    • Acknowledge relapse is inevitable
Refining and Evolving

• Two way street
  – Human needs
  – Environmental press
  – Technological advances
  – Resource allocations
  – Effectiveness and efficacy reviews
  – Life cycle of theories