Accelerating Translation at Dana-Farber Cancer Institute*

*and our partner institutions

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Dana Farber Cancer Institute

Academic Structure

- **All Dana-Farber faculty are also faculty in departments at one of the Harvard schools**

- **Dana-Farber has 8 internal departments**
  - Medical Oncology
  - Pediatric Oncology
  - Radiation Oncology
  - Psychosocial Oncology and Palliative Care
  - Imaging
  - Cancer Biology
  - Cancer Immunology and AIDS
  - Biostatistics and Computational Biology

- **Pediatric oncology care delivered through Jimmy Fund Clinic & divisions in Boston Childrens Hospital**
  - Organized in programs & disease centers
- **Medical oncology care delivered through 12 Disease Centers**
  - Anatomically based Disease Ctrs
  - Early Drug Development Center
- **Disease Centers are sites of clinical trial activity**
- **Clinical trials managed through Dana-Farber/Harvard Cancer Center (DF/HCC)**
  - Consortium of 5 hospitals (DFCI, BIDMC, BWH, BCH, MGH) and 2 Harvard schools (HMS, HSPH)
  - Single IRB oversees trials at all 5 hospitals

DFCI's Research Model

- **Faculty laboratory & research group leaders are "independent contractors"**
  - DFCI provides support for unfettered discovery research
  - Recruitment focused on "best athlete"

- **Amended model needed**
  - Pace of translation of research findings to clinical impact too slow
  - DFCI recognized need to introduce concepts of project management into academic translational research

- **DFCI Strategic Planning**
  - Goal: implement project management principles to translate discoveries into clinical benefit while preserving the culture of independent discovery
  - Faculty identified 10-12 areas ripe for translation
  - Created "Integrative Research Centers" around each

Integrative Research Centers

- **Integrative Research Centers**
  - Combination of technology platform & intellectual hub – not cores
  - Membership crosses departmental boundaries

- **DFCI Centers**
  - Center for Cancer Genome Discovery
  - Center for Functional Cancer Epigenetics
  - Center for Cancer Systems Biology
  - ***Belfer Institute for Cancer Sciences***
  - ***Center for Novel Experimental Therapeutics***
  - ***Center for Molecular Oncologic Pathology***
  - ***Center for Biomedical Imaging in Oncology***
  - Cancer Vaccine Center
  - Center for Cancer Computational Biology
  - Center for Population Sciences
  - Blais Proteomics Center

Integrative Research Centers

- **Founded on business rules & accountability**
  - Faculty leader of each Center charged with developing a business plan
  - Business plan included explicit milestones & deliverables over 5 years
    - » Deliverables built around specific project endpoints rather than academic metrics
  - Financial plan required to bring Center to self-sufficiency within 5 years

- **Incentivizing "independent contractor" faculty to lead Centers**
  - Seed funding to start Center activities
    - » Not released until business plan approved by President
  - Research scientist hiring track
    - » Non-tenure track faculty with project management experience
    - » Rigorous promotion ladder & opportunities for responsibility & advancement
    - » Over 100 research scientist faculty members

- **Oversight**
  - VP for Strategic Planning & CSO for day-to-day
  - Internal Oversight Committees & External Advisory Boards

Program in Cancer Chemical Biology

- **Started as pilot with 3 recruited faculty**
  - All 3 have materials discovered & synthesized in their labs already in clinical trials or about to enter clinical trials
  - Wide diversity of targets & chemistry
    - » Kinase inhibitors, bromodomain inhibitors, stapled peptides

- **Expansion**
  - Leasing research space near Dana-Farber that includes 50,000 sf fit out for chemistry
  - Plan ro recruit

Dana-Farber Support for Highly Predictive Preclinical Models, Biomarkers and Imaging

State-of-the-art experimental therapeutics facility

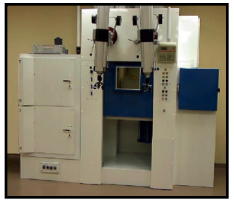
MRI

Optical

Ultrasound

PET/ SPECT/CT

Radio-chemistry



14,000 sq ft
3,300 cages

Full spectrum of mouse cancer models:

- Genetically Engineered Mouse Models
- Primary xenografts
- Cell line xenografts

Full treatment options:

- Expert technical support (7 days/week)
- Radiotherapy

Full spectrum of endpoints:

- Anatomic and molecular functional imaging
- Conventional metrics
- Access to mouse histopathology

Expert design and data analysis:

- Physicists
- Biostatisticians

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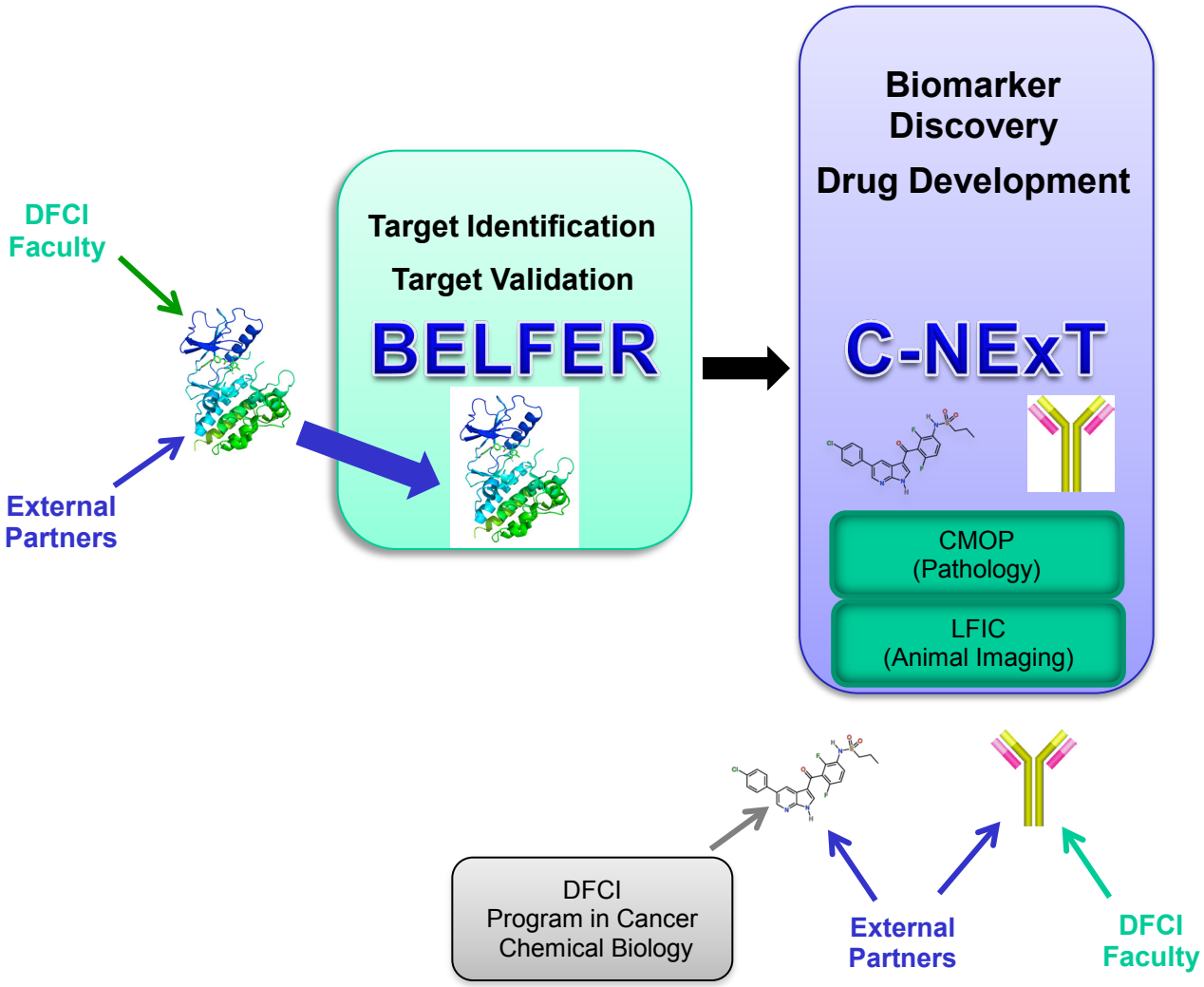
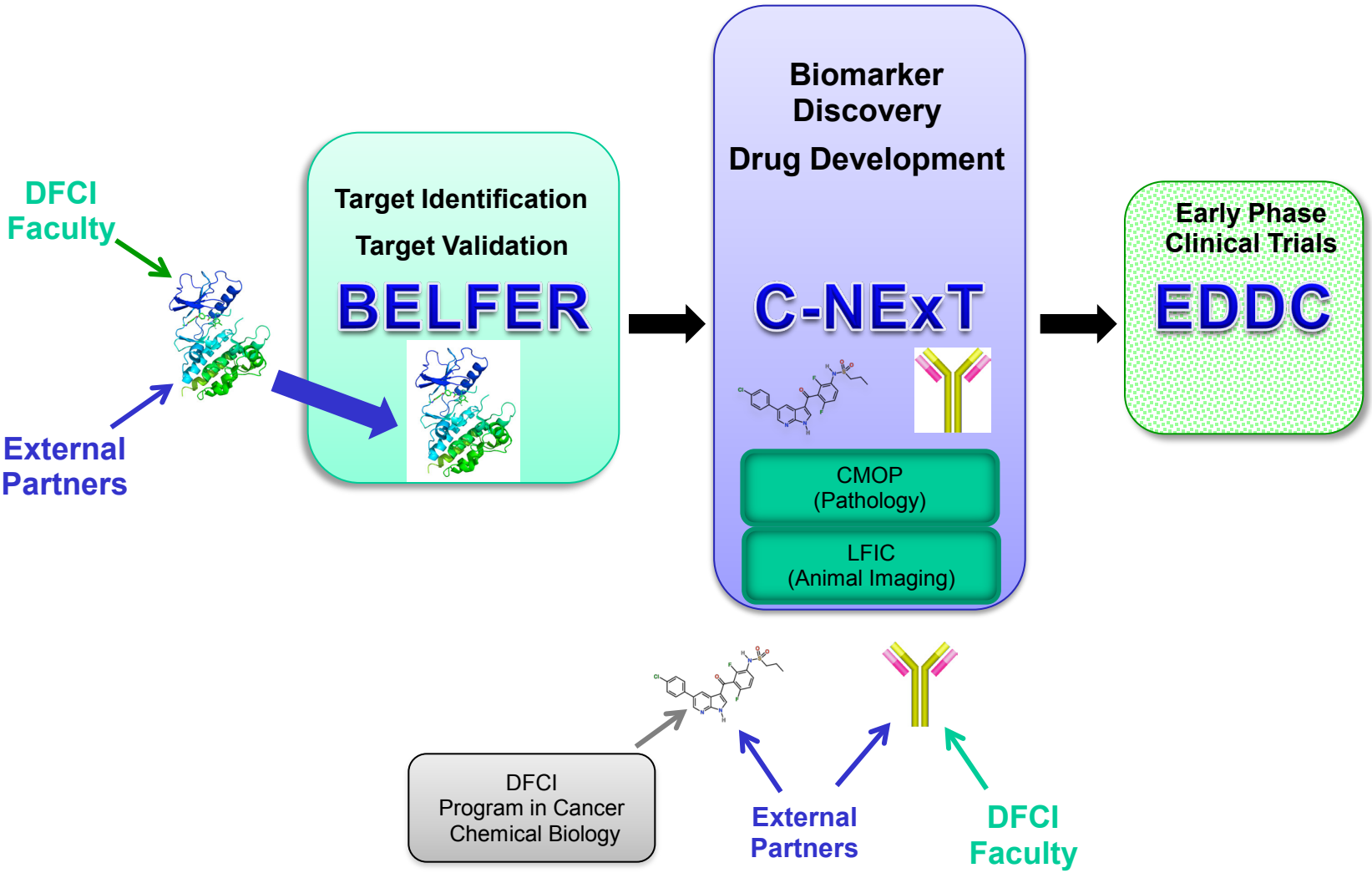
Drug Development in Integrative Research Centers



Drug Development in Integrative Research Centers



The Belfer Institute Bridges the Gap Between Academia & Industry

- Provide goal-oriented milestone-driven structure on academic activity
- Co-Scientific Directors Pasi Janne MD PhD & Kwok Wong MD PhD
  - Recognized leaders in the development of targeted therapies for lung cancer
- 45+ dedicated professional staff members
  - Industry/Academia hybrid organization: leadership from industry
- In depth target biology required to move programs through drug discovery pipeline
- Expertise in modeling: GEMM, non-germline and orthotopic systems, primary tumor xenografts, short-term cultures
- Expertise in biomarkers: Experienced with clinical biomarker assays
- Access to clinical specimens through academic collaborations: Broad network of investigators/collaborators: DFHCC TCGA, Broad

Belfer Institute Partnering with Large Pharma
Impact across pipeline

Drug Discovery Pipeline

Identifying/ Validating New Targets

- ***CSS screens***
- ***shRNA screens, in vitro/in vivo***

Prosecuting New Targets

- ***Novel targets from DFCI Labs***

Delineating Clinical Path for Drugs in Clinical Trials

- ***Delivered IND enabling data package***
- ***Demonstrated efficacy of proprietary combo***

Novel targets identified

TCGA + Screening data= dependency confirmed upfront

DFCI Investigator with disease expertise part of team

Belfer validating target using industry standards

Team: Belfer + Pharma Scientists & DFCI Investigator

Innovation to address clinical problems: Blood Based Biomarkers

Recent Clinical Studies with Blood Based Biomarkers

3 Pharma → **5 Clinical Trials** →

- **Determine mutational status**
  Goal: match patients to drugs
- **Identify new biomarkers**
- **Evaluate novel technology in clinical setting**

- Trials combine academia innovation on novel quantitative biomarkers & with testing of industry agents targeting resistance
- Develop the tools needed to advance novel therapies targeting resistance

Belfer Institute for Applied Cancer Science: Industry Collaborations

Integrating DFCI Investigators in all programs

- Novel Targets & Drug Discovery work with Pharma
  - Target ID
  - Target Validation
  - Target Prosecution
    - Work on disease biology as molecules are being refined
      - Responder ID hypothesis
      - Target engagement biomarkers
- Existing Pharma Clinical Stage Molecules
  - Delineating Clinical Combinations
    - IND enabling clinical combination *in vivo* data set
  - Blood Based Biomarkers
    - Biomarkers for non invasively, real-time, tracking of resistance

Comprehensive Preclinical/Translational Lung Experimental Therapeutics Program

Past examples of direct translation of GEMM preclinical data into human clinical trials

- **EGFR**: Neratinib plus rapamycin combination (phase I trial at DFCI) (Cancer Cell 2007)
- **EGFR, HER2**: BIBW2992 plus rapamycin combination (phase1 trial in Europe)(Oncogene 2008 and PNAS 2009)
- **KRAS, EGFR, p110**: p110 inhibitor plus MEK inhibitor combination (Multiple Phase I trials at DFCI) (Nature Medicine 2008, PNAS 2010)
- **KRAS, EGFR, EML4-ALK**: HSP90 inhibitor (multiple phase I trials at DFCI) (Cancer Research 2008, 2011 and Cancer Cell 2011)
- **EGFR**: ABT806 antibody (phase I trial at DFCI) (JCI 2008)
- **KRAS, BRAF**: MEK (AZD6244) inhibitor in BRAF lung cancer patients (phase I trial at DFCI) (Cancer Research 2007)
- **KRAS, p53, LKB1**: MEK(AZD6244) inhibitor and Docetaxel in KRAS lung cancer patients (phase II trial) (Nature, 2012)

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previous article next article

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Articles

Selumetinib plus docetaxel for *KRAS*-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study

Dr Pasi A Jänne, MD[a], Alice T Shaw, MD[b], José Rodrigues Pereira, MD[c], Gaëlle Jeannin, MD[d], Prof Johan Vansteenkiste, MD[e], Carlos Barrios, MD[f], Fabio Andre Franke, MD[g], Lynda Grinsted, MSc[h], Victoria Zazulina, MD[h], Paul Smith, PhD[h], Ian Smith, MD[h], Prof Lucio Crinò, MD[i]

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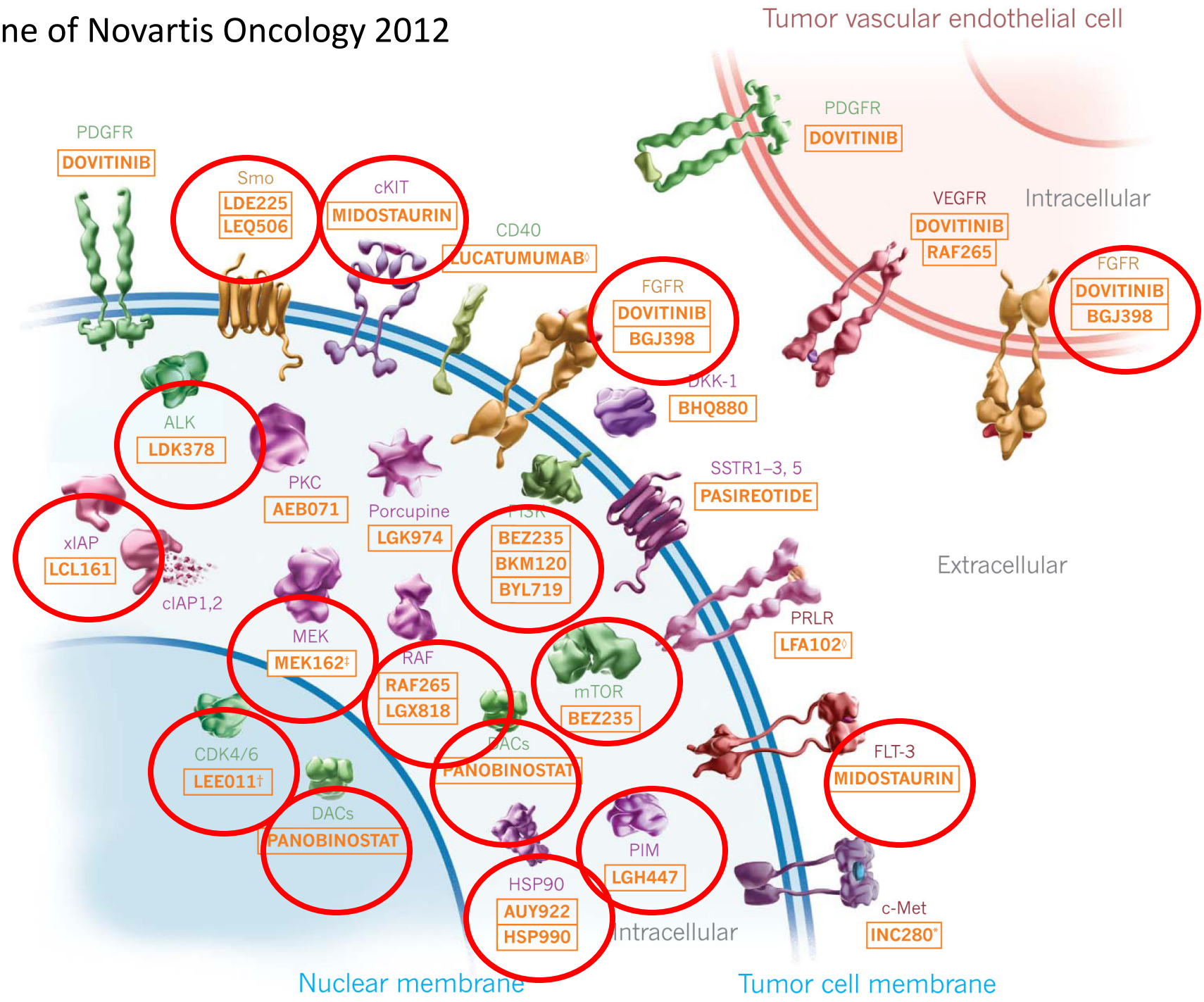
How the Collaboration Works

- Novartis publishes an RFA on topics they are interested in supporting
- DFCI investigators submit applications which are peer-reviewed by DFCI and Novartis scientists
- Some projects focus on new target identification and validation
- Others emphasize collaboration on projects already established at Novartis including evaluation of lead compounds

Pipeline of Novartis Oncology 2012



Capabilities for Translational Research

DANA-FARBER CANCER INSTITUTE

DISEASE CENTERS
- Bone and Sarcoma
- Cancer Genetics
- Cutaneous and Mohs Surgery
- Gastrointestinal
- Women's Cancers
- Head and Neck
- Genitourinary
- Thoracic
- Hematology
- Neuro
- Experimental therapeutics
- Psychosocial

INTEGRATIVE RESEARCH CENTERS
- Center for Cancer Vaccines
- Center for Translational Research
- Center for Population Sciences
- Center for Experimental Pathology
- Center for Cancer Genomics
- Center for Cancer Systems Biology
- Center for Applied Cancer Science

TECHNOLOGIES
- Proteomics
- Genomics
- Chemistry
- Computational Biology
- Imaging

INVESTIGATORS
- Basic
- Translational
- Clinical