Challenges to Drug Development in Academia

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Disclosure

I am a co-inventor of the drug MDV3100, now in a phase III clinical trial in prostate cancer, and I own stock in the company Medivation.
Two translational tales

1) Dasatinib (Sprycel) in chronic myeloid leukemia:
   serendipitous marriage of a discovery in academia that reshaped a pharma-driven drug development program

2) MDV3100 in prostate cancer:
   academia-based target validation and drug screening project that resulted in a biotech/pharma licensing deal for clinical development
The Ph Chromosome: t(9;22) Translocation

FUSION PROTEIN WITH TYROSINE KINASE ACTIVITY

Normal

CML
Imatinib/STI571 (Gleevec) blocks BCR-ABL

Goldman JM, Melo JV. *NEJM*. 344:1084-1086
Blood counts of the first 6 patients who took 300 mg/day of Gleevec
Gleevec is not a cure:

Small numbers of CML cells are detected in patients who are in “remission.”

Patients can relapse while taking Gleevec.

Why?
A mutation isolated from patients who relapse on Gleevec blocks drug binding to BCR-ABL

(Gorre et al. Science, 2001)
BCR-ABL Kinase Domain Mutations
Associated with Imatinib Resistance

T315I


M244V  D276G  T277A  E279K  M351T  E355G/D  V379I  S417Y  F486S

> 50 distinct mutations reported
Imatinib resistance mutations impair conformational flexibility of the ABL kinase

Location of Mutations
- P loop
- Direct contact with drug
- Hinge

John Kuriyan, Bhushan Nagar (UC-Berkeley)
How do we deal with resistance?

**Problem:** Over 50 different mutations can cause resistance to Gleevec

**Structural biology prediction:** Mutations change the shape of BCR-ABL so that it favors the “open” conformation.

**Solution:** Drugs that target the “open” conformation should work in patients with Gleevec resistance.
The SRC/ABL inhibitor dasatinib (BMS-354825) is active against all but one of the known mutations in BCR-ABL that confer imatinib resistance.

Shah et al Science, 2004
BCR-ABL genotype predicts clinical response to dasatinib

Talpaz ….Sawyers, NEJM, 2006
1) Imatinib has been frontline CML therapy

- 75% of patients achieve complete cytogenetic response
- 20% relapse within 5 years, usually with mutant BCR-ABL

2) Dasatinib and nilotinib were initially approved as 2nd line therapy for imatinib-resistant CML (2006, 2007)

3) Upfront comparisons show than 2nd generation compounds are superior to imatinib
   (Kantarjian et al NEJM 2010; Saglio et al NEJM 2010)
Inhibition of androgen receptor (AR) signaling

**Testosterone hormone**

**LHRH agonists**

**AR kinases**

**Anti-androgens**

- Bicalutamide*
- Flutamide*

*Both drugs are partial agonists/antagonists

**Androgen receptor**

**CoR vs Coactivators**

**NCoR/HDAC**

**Pol II**

**Transcription of AR target genes eg PSA**

**Activation of TMPRSS/ERG fusion**
Typical Response to Hormone Therapy

- Disease Burden
- Time
- Hormone Therapy
- Discontinue Antiandrogen
Primary Mechanism of Resistance to Castration and/or Current Antiandrogens

1) AR is overexpressed in castration resistant sublines of multiple prostate cancer xenograft models (and in patients)
2) Forced AR overexpression confers castration-resistance
3) AR knockdown impairs castration-resistant growth
4) AR antagonists act as agonists when AR levels are high (Chen et al Nature Med, 2004)
AR is required to maintain castrate resistance in vivo

AR RNAi

Lentivirus vector

5’ LTR

U6

AR RNAi

Term.

CMV

GFP

3’ LTR

Growth of castrate resistant xenografts in castrate male mice
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Second generation anti-androgens must:

- be effective in cells expressing high levels of androgen receptor
  AND
- overcome the problem of antagonist/agonist conversion
Cell-based screen for compounds with greater antagonism and no agonism ("pure antagonists")

Design tools:
- Crystal structure
- Homology modeling
- Binding affinity

High AR binding affinity ($K_a = 20$ nM for human AR)
But with agonistic activity

Hydrophobic interactions with AR
Antagonist Activity
Jung et al, J Med Chem, 2010

Samedy Ouk, Michael Jung (UCLA Department of Chemistry)
RD162 and MDV3100 do not display agonism in AR overexpressing cells

...and have more potent antagonist activity

Tran et al, Science 2009
RD162 (and MDV3100) are superior to bicalutamide in the castrate-resistant LNCaP-AR xenograft model.

Immunodeficient SCID castrate male mice. Tumor volume was measured in 3 dimensions.

Tran et al, Science 2009
Androgen receptor activation and mechanism of antiandrogen action

Overlap among AR binding peaks in response to antagonists (determined by AR ChIP-Seq)

peaks found by MACS, p-value <10^{-5}

Ling Cai
A Phase 1-2 Multicenter First-in-Man Trial of MDV3100 in Castrate Resistant Prostate Cancer

1. Dose escalation, 3 patients per cohort, beginning at 30 mg/d to 600 mg/d
2. After safety was established at 60 mg/d, cohorts were expanded to 24 patients (12 chemo-naïve, 12 chemo failure)
3. First patient dosed in July, 2007
4. 140 men enrolled at 5 centers
   (MSKCC, OHSU, U Wash, DFCI, MDACC)

Scher et al Lancet, 2010
Waterfall Plot of Best Percent PSA Change from Baseline

Chemotherapy-Naïve (N=65)

62% (40/65) ≥50% Decline

Post-Chemotherapy (N=75)

51% (38/75) ≥50% Decline
## Radiographic Changes in Soft Tissue (N=59) and in Bone (N=109)

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy-Naïve Patients (N=65)</th>
<th>Post-Chemotherapy Patients (N=75)</th>
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<tbody>
<tr>
<td><strong>Soft Tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Best Response)</td>
<td>N=25</td>
<td>N=34</td>
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<tr>
<td>Partial Response</td>
<td>36% (9/25)</td>
<td>12% (4/34)</td>
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<tr>
<td>Stable Disease</td>
<td>44% (11/25)</td>
<td>53% (18/34)</td>
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<tr>
<td><strong>Bone Scan (Week 12)</strong></td>
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<tr>
<td>Stable Disease</td>
<td>63% (26/41)</td>
<td>51% (35/68)</td>
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</tbody>
</table>

*59 patients with evaluable soft tissue disease as defined by PCWG2 consensus J Clin Oncol 2008.*
Time to PSA Progression For Pre- and Post-Chemotherapy Treated Patients

Pre (Not reached)

Post (186 days)
Summary

1. Castration resistant prostate cancer remains dependent on androgen receptor (AR) function.

2. Pure AR antagonists like MDV3100 can overcome clinical resistance to partial antagonists (bicalutamide).

3. MDV3100 likely induces an AR conformation that precludes DNA binding.

4. MDV3100 development has progressed to a phase III registration trial in castration resistant, chemotherapy resistant prostate cancer.
CML/Abl Inhibitor Project

Mercedes Gorre  Neil Shah  Mike Burgess  John Nicoll  Chris Tran

BMS clinical trial
Moshe Talpaz
Art Decillis
Claude Nicaise
Eric Bleickardt

Collaborators
Bhushan Nagar
John Kuriyan
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Frank Lee (BMS)
Prostate Cancer/Antiandrogen Project

Charlie Chen  Derek Welsbie  John Wongvipat  Chris Tran

Nicola Clegg  Michael Jung (Chemistry)  Samedy Ouk (Chemistry)

David Hung
Medivation