FNIH Biomarkers Consortium Adiponectin Project

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“Competitors share early stages of research that benefit all”

Precompetitive collaboration is increasingly recognized as a driver for enhanced efficiency, while simultaneously increasing our grasp of heightened complexity.
A Precompetitive Collaboration
Goals of
The Biomarkers Consortium

- Facilitate the development and validation of biomarkers using new and existing technologies

- Help qualify these biomarkers for specific applications in diagnosing disease, predicting therapeutic response, or improving clinical practice

- Generate information useful to inform regulatory decision-making

- Make consortium project results broadly available to the entire scientific community

www.biomarkersconsortium.org
Biomarker: Adiponectin

Kusminski, Scherer, CPT 2009;86 6, 592–595

Can adiponectin predict HbA1c response in patients with type 2 diabetes?

Patient segmentation may drive more effective PPAR use.

A number of pharmaceutical companies have conducted PPAR research:

- Isolated datasets in individual companies
- Relatively sparse publications

Could the biomarkers consortium be used to facilitate a cross-company, pre-competitive collaboration to answer the research question?
Adiponectin as a Biomarker Predictive of Glycemic Efficacy

Blinded data from pre-existing clinical trials pooled (~ 2000 pts)

- **Phase 1**
  Baseline evaluation to confirm the validity of the dataset

- **Phase 2**
  Evaluate change of adiponectin vs. change of the other variables

- **Phase 3**
  Examine prognostic value change in adiponectin at "early" times to predict HbA1c response

GSK
Lilly
Merck
Roche

Analysis
NIDDK
Analysis
Quintiles

Results Review
Biomarkers Consortium Project Team

Results made public
Adiponectin Project: Results

Phase 3: Examine prognostic value change in adiponectin at "early" times to predict HbA1c response
follow-up correlations of change in adiponectin and glucose at 6-8 weeks with change in HbA1c at 24-52 weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Correlation</th>
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<tbody>
<tr>
<td>Adiponectin</td>
<td>-0.21 (p&lt;0.0001)</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>0.49 (p&lt;0.0001)</td>
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Wagner et al, CPT 86:619-25, 2009
ROC Curves for Prediction of HbA1c Response at 24 to 52 Weeks

Responder: Decrease in HbA1c ≥ 0.7

BLUE – Model includes baseline adiponectin and change from baseline in adiponectin
AUC: 0.79

GREEN – Model includes baseline glucose and change from baseline in glucose
AUC: 0.82

Wagner et al, CPT 86:619-25, 2009
Adiponectin project highlights

• Conclusions
  – Adiponectin is a robust predictor of glycemic response to PPAR agonists, but not non-PPAR drugs, in T2D patients
  – Previous findings about the relationship between adiponectin levels and metabolic parameters (HbA1C, HDL, hematocrit) were confirmed by this analysis
  – The potential utility of adiponectin across the spectrum of glucose tolerance was demonstrated
  – This project established that cross-company collaboration was a robust, feasible and powerful approach to biomarker qualification

Wagner et al, CPT 86:619-25, 2009
Lessons learned

Project Concept Submitted to BC

Concept Approval By MDSC

Project Team Formed

Clinical trials With Relevant Data Identified By 4 Companies

Data Sharing/Confidentiality Agreements Developed and Executed

Project Launch

Phase I & II Data Analysis

Analysis Of All Available Results

Phase III Data Analysis

Manuscript And Presentation Preparation

Wagner et al, CPT 87:539-42, 2010
### Lessons learned

<table>
<thead>
<tr>
<th>Issue</th>
<th>Lesson</th>
<th>Mitigation</th>
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<tbody>
<tr>
<td>Focus, organization and pace</td>
<td>Though ultimately successful, the overall project was lengthy</td>
<td>Robust project management with accountable leaders</td>
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<tr>
<td>Optimal collaboration</td>
<td>A lack of collaboration tools hampered the project</td>
<td>Collaboration web portal</td>
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<td>Data-sharing principles and standards</td>
<td>A uniform, legally-appropriate data-sharing plan was difficult to negotiate</td>
<td>Regular meetings, face-to-face</td>
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<td></td>
<td>Standard definitions were not always obvious and clearly important</td>
<td>Adequate time and resources</td>
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<td>Limited institutional memory</td>
<td>The template for Biomarkers Consortium data-sharing plan and confidentiality is now available</td>
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<tr>
<td>Limitations of existing data</td>
<td>The retrospective dataset lacked time points earlier than 6 weeks of dosing, which limited the ability to make conclusions related to the prognostic value of the biomarker</td>
<td>Acknowledge limitations</td>
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<tr>
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<td>Blinded aggregated data is inherently limited, including in this case difficulties with specifying dose response</td>
<td>Prospective follow-up when necessary</td>
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<td>Different biomarker assays</td>
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Wagner et al, CPT 87:539-42, 2010
Lessons learned

• Issues

- Clarity of question defines the type of collaboration
- Key role of the neutral convener
- Dialogue with FDA early and often
- Behaviors driving / impeding precompetitive collaboration
- “Collaborations” often siloed, incomplete, or excessively transactional
- Motivations are similar and different across stakeholders sometimes creating real or potential conflicts, including intellectual property, conflict-of-interest, appropriate rewards, publications, and culture
Lessons learned

• Progress
  ✓ Clarity of question defines the type of collaboration
  ✓ Key role of the neutral convener
  ✓ Dialogue with FDA early and often

☐ Behaviors driving / impeding precompetitive collaboration
  ▪ Key role of trust, openness
  ▪ Increase communication / transparency among collaborating partners

☐ “Collaborations” often siloed, incomplete, or excessively transactional
  ▪ We can improve collaboration by recognizing our common goals and the unique value of each party
  ▪ Collaborations cannot and should not be defined as providing unrestricted grant dollars
  ▪ Defined and productive research relationships between industry and academia will emerge if both identify common goals
  ▪ Need to strive for open inclusiveness in appropriate collaborations

☐ Motivations are similar and different across stakeholders
  ▪ Better align stakeholder interest and rewards
  ▪ “You get what you reward”
Acknowledgments

Adiponectin Project Team / Collaborators
Elizabeth Wright, NIDDK/NIH
Michele Ennis, Quintiles
Sujoy Ghosh, GSK
Jarema Kochan, Roche
Derek Nunez, GSK
Melvin Prince, Lilly
Bruce Schneider, CBER/FDA
John Wagner, Merck
Ming-Dauh Wang, Lilly
David Fryburg, Pfizer
Yu Chen, Merck
Brett Musser, Merck
Jose Velasquez, NIA/NIH

IOM Precompetitive Collaboration
Jill Altshuler, AltshulerGray
Erin Balogh, IOM
Anna Barker, NCI
Stephen Eck, Lilly
Stephen Friend, Sage Bionetworks
Geoffrey Ginsburg, Duke
Roy Herbst, Yale
Sharon Murphy, IOM
Sharyl Nass, IOM
John Wagner, Merck

MDSC Scientific Program Manager
Maria Vassileva, FNIH

Extending the Spectrum of Precompetitive Oncology Biomedical Research (February 9-10, 2010)