# FNIH Biomarkers Consortium Adiponectin Project

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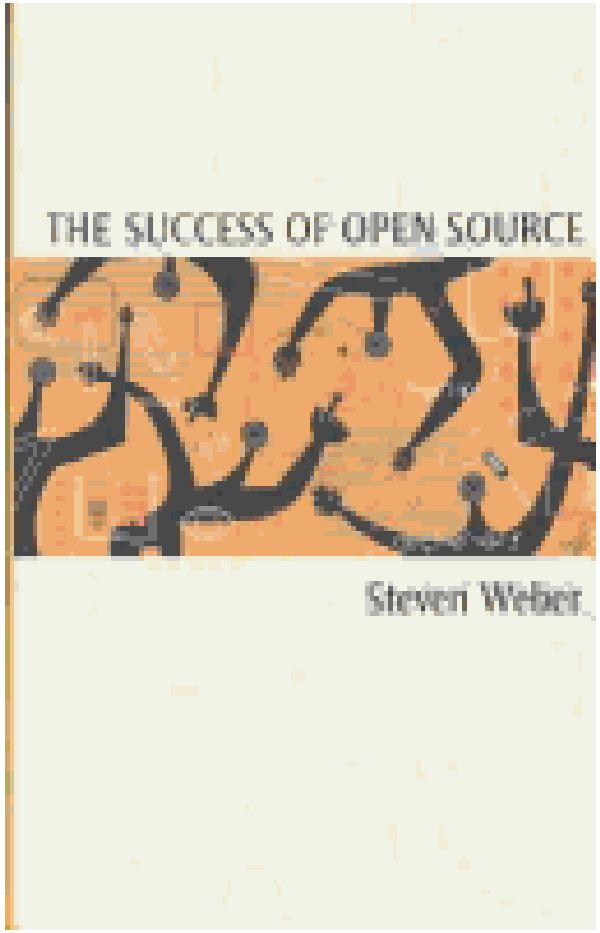
# Precompetitive collaboration




- “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

Weber, The success of open source, 2004


# A Precompetitive Collaboration

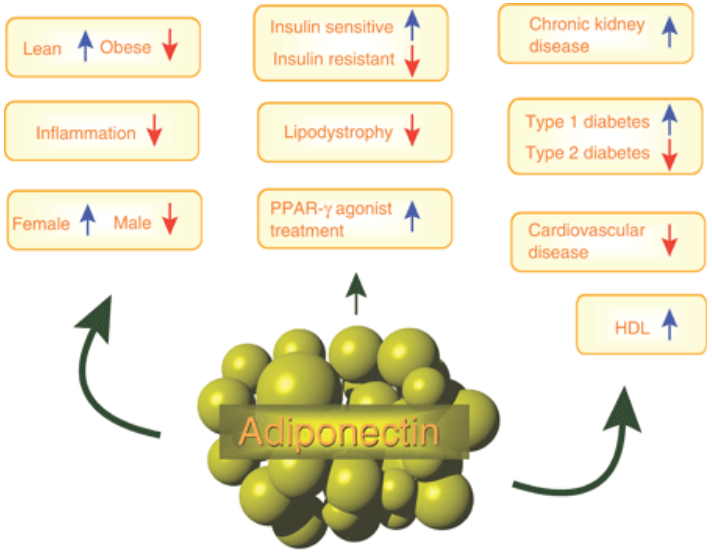




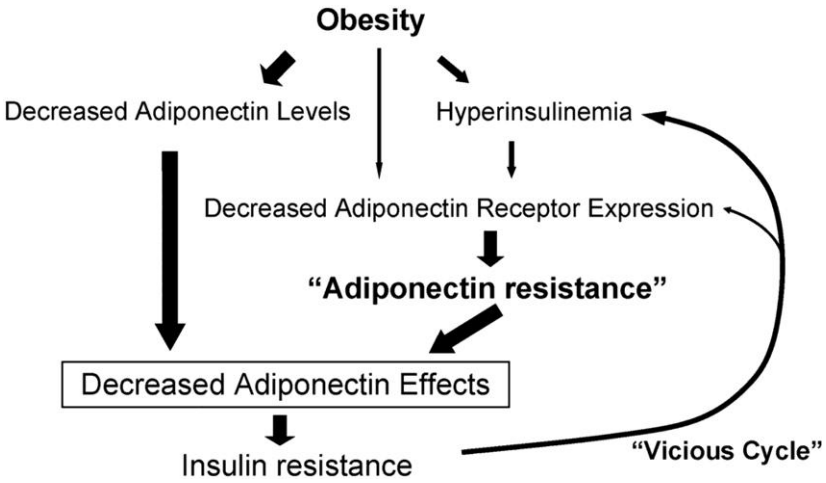

# Goals of The Biomarkers Consortium

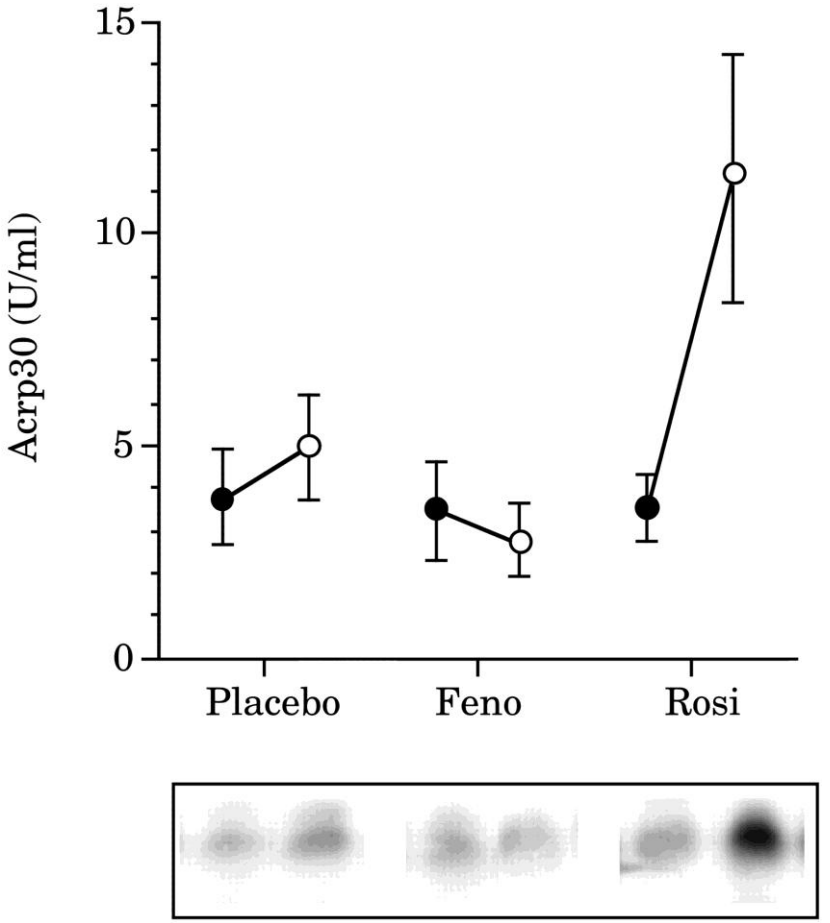
- Facilitate the development and validation of biomarkers using new and existing technologies
- Help qualify these biomarkers for specific applications in diagnosing disease, predicting therapeutic response, or improving clinical practice
- Generate information useful to inform regulatory decision-making
- Make consortium project results broadly available to the entire scientific community

# Biomarker: Adiponectin




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





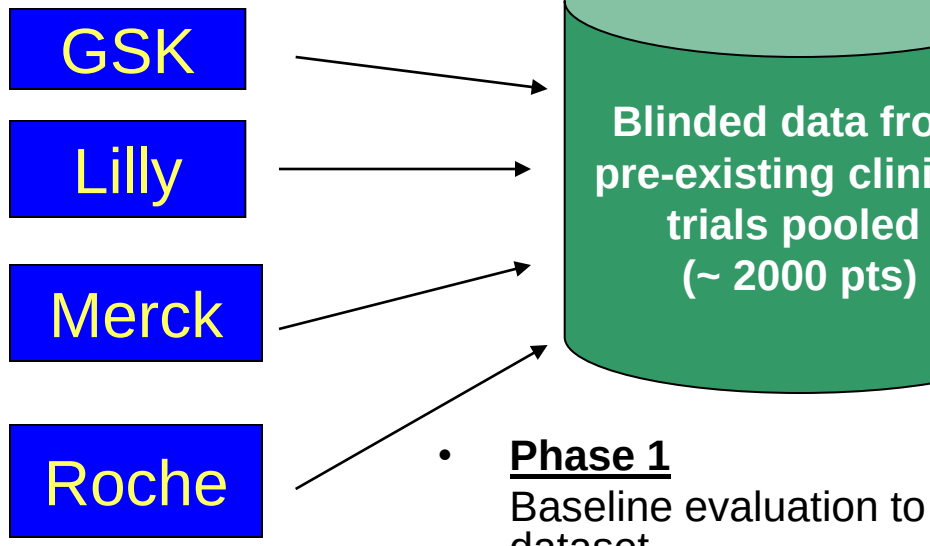

Kadowaki T , Yamauchi T Endocrine Reviews 2005;26:439-451 Combs T P et al. Endocrinology 2002;143:998-1007

# Adiponectin Project


- 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

THE biomarkers CONSORTIUM




- **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

# Adiponectin Project: Results

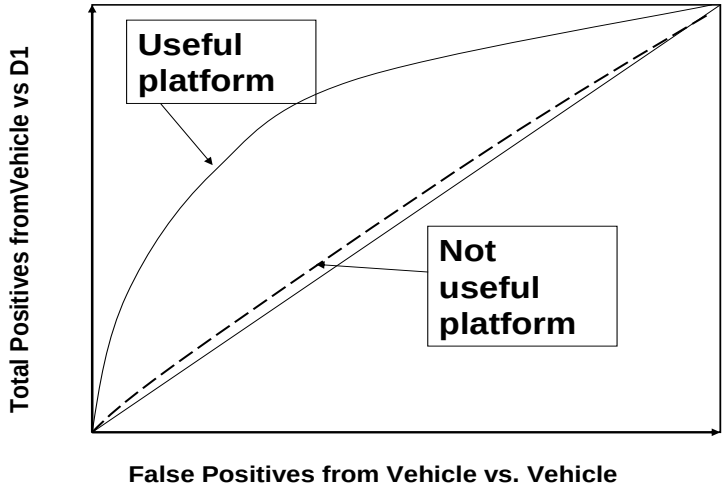
**Phase 3: Examine prognostic value change in adiponectin at "early" times to predict HbA1c response**
**follow-up correlations of change in adiponectin and glucose at 6-8 weeks with change in HbA1c at 24-52 weeks**

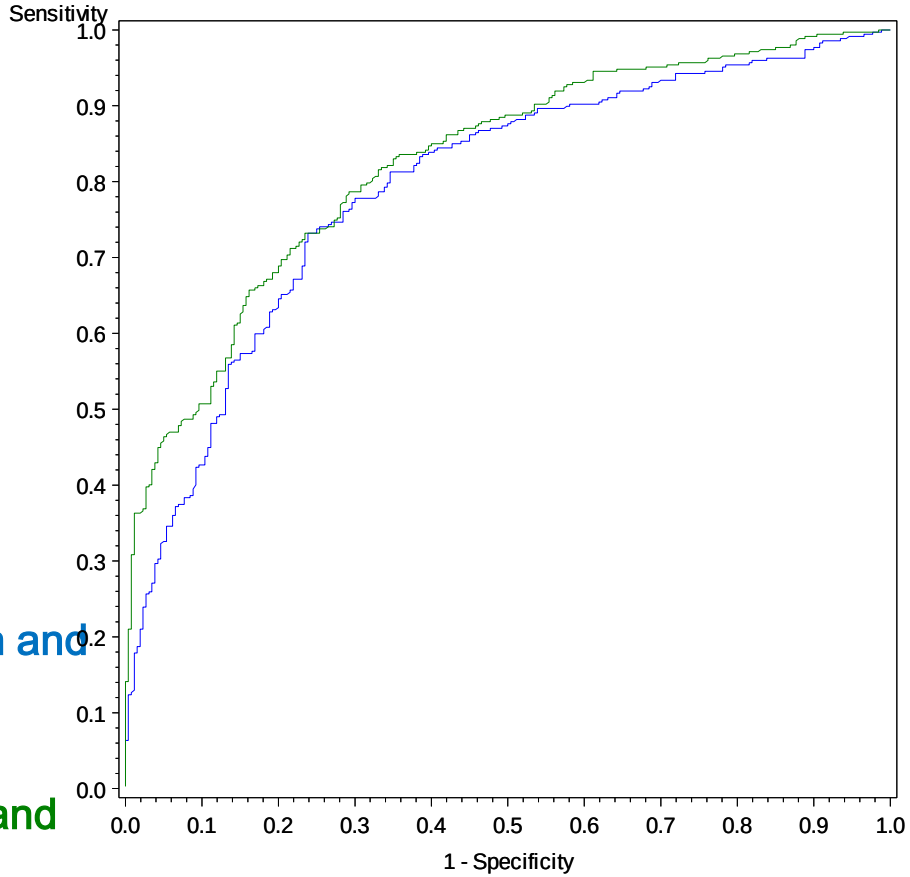
| Variable | Correlation |
|---|---|
| Adiponectin | -0.21 ($p<0.0001$) |
| Fasting Glucose | 0.49 ($p<0.0001$) |

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

# ROC Curves for Prediction of HbA1c Response at 24 to 52 Weeks

## Figure of Merit (ROC curves)




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

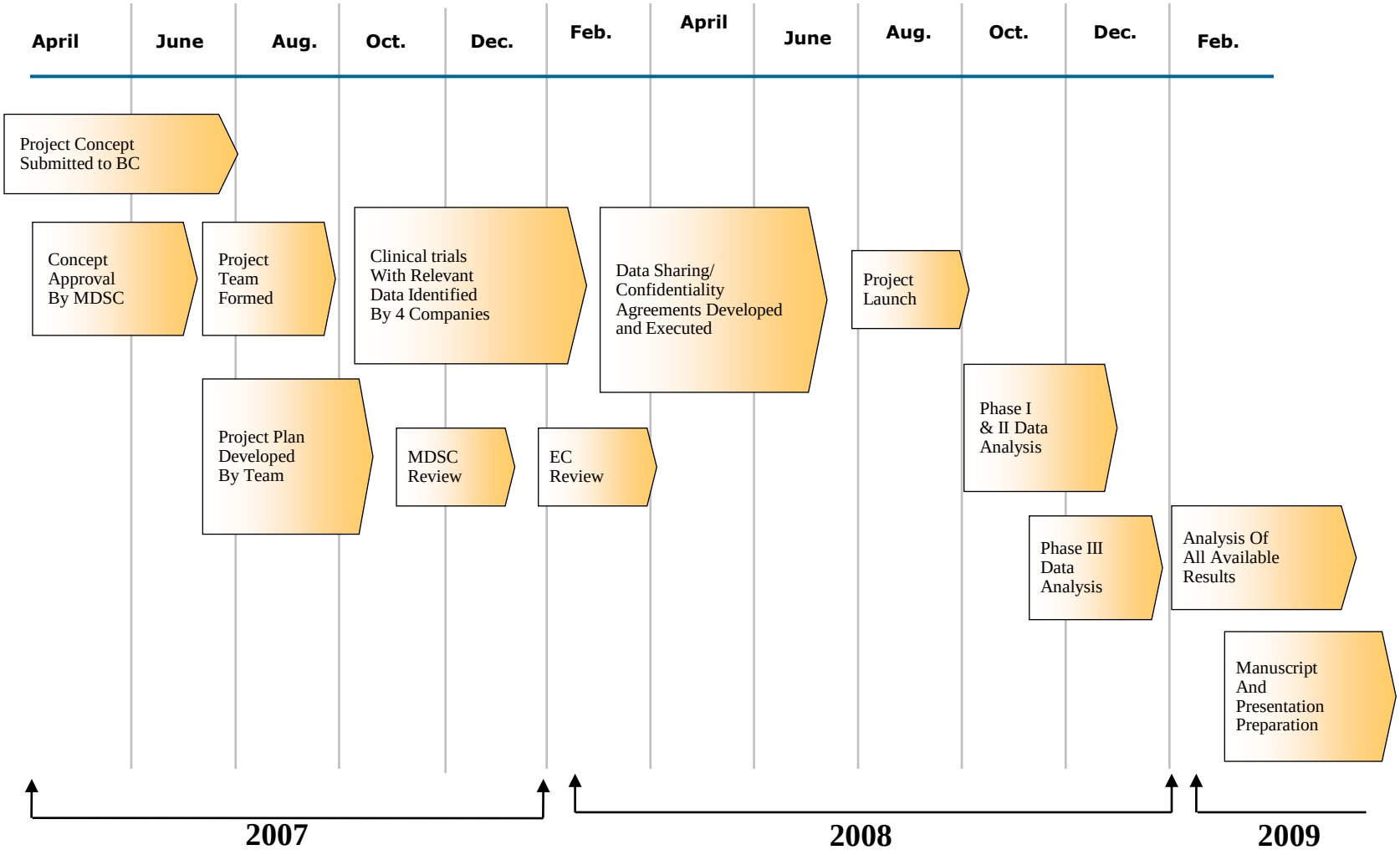
Wagner et al, CPT 86:619-25, 2009

# 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




Wagner et al, CPT 87:539-42, 2010

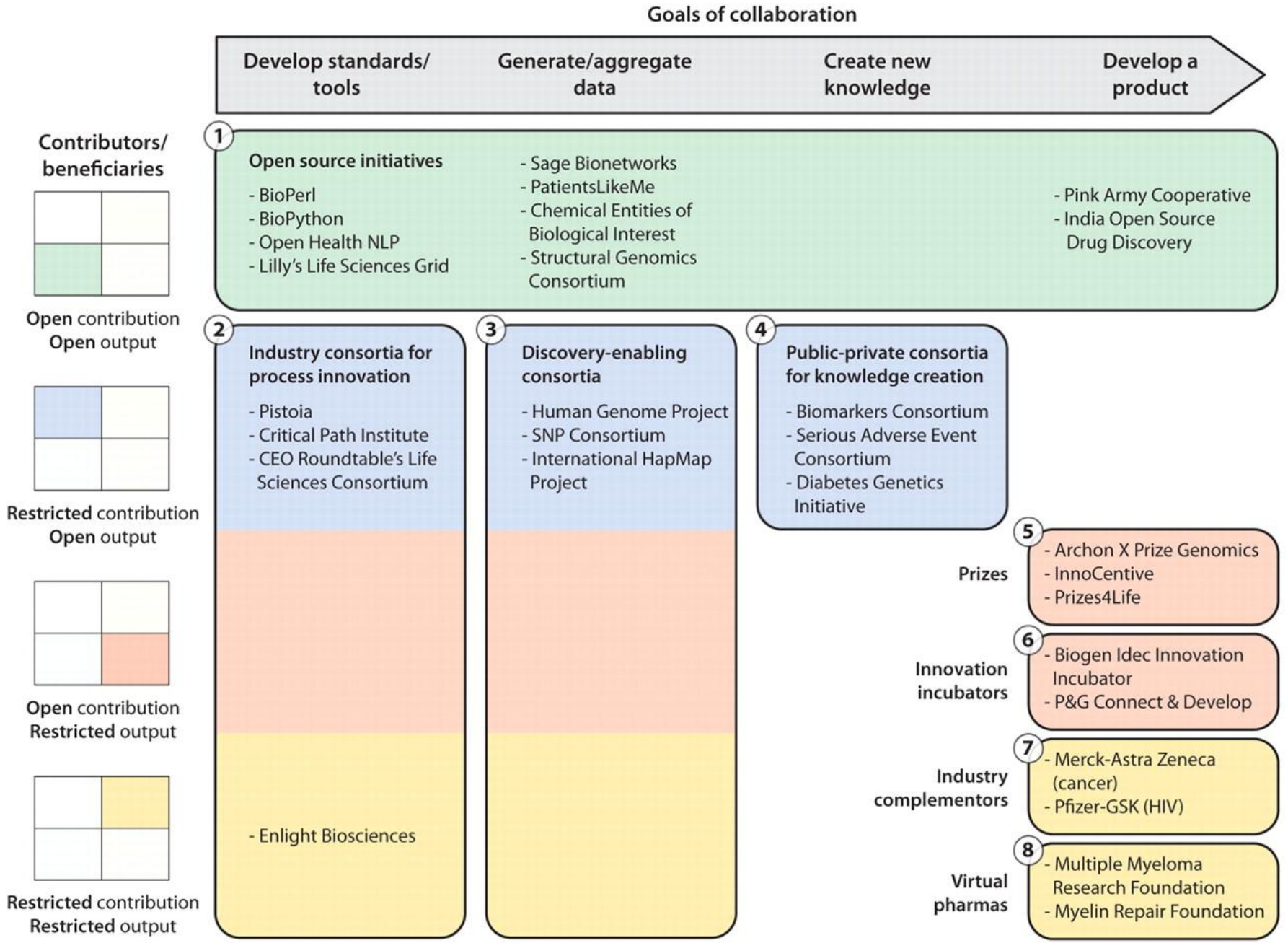
# Lessons learned

| Issue | Lesson | Mitigation |
|---|---|---|
| Focus, organization and pace | Though ultimately successful, the overall project was lengthy | Robust project management with accountable leaders |
| Optimal collaboration | A lack of collaboration tools hampered the project | Collaboration web portal<br><br>Regular meetings, face-to-face |
| Data-sharing principles and standards | A uniform, legally-appropriate data-sharing plan was difficult to negotiate<br><br>Standard definitions were not always obvious and clearly important<br><br>Limited institutional memory | Single accountable legal liaison<br><br>Adequate time and resources<br><br>The template for Biomarkers Consortium data-sharing plan and confidentiality is now available |
| Limitations of existing data | 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<br><br>Blinded aggregated data is inherently limited, including in this case difficulties with specifying dose response<br><br>Different biomarker assays | Acknowledge limitations<br><br>Prospective follow-up when necessary |

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




Altshuler et al Sci Transl Med 2010;2:52cm26-52cm26

Science Translational Medicine AAAS

# 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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