Academic Industry Relations: A Cardiovascular Clinical Trialists Personal Perspective (The GOOD and The BAD)

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Consultant: Bayer, Astra Zeneca, Sanofi, Merck, Relypsa/Vifor*, Sarfez*, ScP Pharmaceuticals*, Sqinnovations* G3Parmaceutiocals*, Cereno Scientific*, Ardelyx

- =stock options
- US Patent 9931412-site specific delivery of Eplerenone to the Myocardium

Academic – Industry Relations
The GOOD and The BAD

The GOOD

"Without industry funding important advances in disease prevention and treatment would not have occurred"

Lee Goldman, Chairman Department of Medicine University of California, San Francisco

The BAD

……why shouldn't clinical researchers have close ties to industry? One obvious concern is that these ties will bias research, both the kind of work that is done and the way it is reported. Researchers might undertake studies on the basis of whether they can get industry funding, not whether the studies are scientifically important. That would mean more research on drugs and devices and less designed to gain insight into the causes and mechanisms of disease. It would also skew research toward finding trivial differences between drugs, because those differences can be exploited for marketing. Of even greater concern is the possibility that financial ties may influence the outcome of research studies"

M. Angel NEJM, 2000

Academic – Industry Relations

The BAD

"I believe the claim that extensive ties between academic researchers and industry are necessary for technology transfer is greatly exaggerated, particularly with regard to clinical research. There may be some merit to the claim for basic research, but in most clinical research, including clinical trials, the "technology" is essentially already developed. Researchers are simply testing it. Furthermore, whether financial arrangements facilitate technology transfer depends crucially on what those arrangements are. Certainly grant support is constructive if administered properly. But it is highly doubtful whether many of the other financial arrangements facilitate technology transfer depends crucially on what those arrangements are. Certainly grist support is constructive if administered properly. But it is highly doubtful whether many of the other financial arrangements facilitate technology transfer or confer any other social benefit"

M. Angel NEJM, 2000

Academic-Industry Relations
My Experience with Cereno Scientific (The GOOD)

- Valproic acid has been used as an anti-epileptic drug for over 50 years
- Danish and Swedish epidemiologists found that epileptic patients on valproic acid had a significantly lower incidence of strokes and myocardial infarction than epileptic patients on other drugs
- Subsequent research found that valproic acid stimulates the release of Tpa and inhibits the release of PAI-1, thus providing an explanation for the reduction in strokes and myocardial infarction
- To take advantage of this finding a small Swedish biotech company, Cereno Scientific, developed a timed release formulation of valproic acid that blocks the morning increase in PAI-1
- The company planned to develop their timed release formulation of valproic acid (CS-1) as an effective anti-thrombotic agent with minimal or no increased bleeding risk
- Initial studies were planned to evaluate its effectiveness and safety as an anti-thrombotic agent in patients undergoing hip surgery to prevent deep venous thrombosis (DVT)

China, 2019

Academic-Industry Relations
My Experience with Cereno Scientific (The GOOD)

- In December 2018 the CEO of Cereno Scientific, whom I had know from his time at Searle during the time I was conducting the RALES trial of Spironolactone in patients with severe HFrEF contacted me through Linkedin and mentioned that Cereno Scientific was developing a timed release formulation of Valproic as an effective and safe antithrombotic agent
- I mentioned to him that CS-1 should have important anti-fibrotic effects since it blocked PAI-1, which is known to have an anti-fibrotic effect in part linked to its effects on aldosterone
- Subsequent review of the literature revealed that valproic acid is an Hdac1 inhibitor and has been shown to block the acetylation of the mineralocorticoid receptor (MR) with a resultant decrease in fibrosis
- There are numerous reports in the literature suggesting that valproic acid inhibits the formation of fibrosis in the vasculature, heart, lungs, live and kidney

Academic-Industry Relations
My Experience with Cereno Scientific (The GOOD)

- Recent studies at the University of Michigan have shown that valproic acid reduces myocardial infarct size and has important organ protective effects. Other preclinical studies have recently shown that valproic acid prevents the development of fibrillation
- As a result of these insights and recent findings Cereno Scientific is now developing CS-1 in a number of indications including: prevention of thromboembolic events in patients with atrial fibrillation as well as prevention of recurrent and persistent atrial fibrillation
- Treatment and prevention of the progression of pulmonary hypertension
- Cereno Scientific is also testing new derivatives of valoproic acid that potentially will be as or more effective in preventing thrombosis and fibrosis with less liver toxicity

Academic-Industry Relations
My Experience with Sanofi-Lexicon (The Bad)

- In 2015 Sanofi paid $30 million up front to Lexicon and committed to up to $1.4 billion in milestone payments to obtain a world wide license to develop Sotagliflozin, a SGLT2/1 inhibitor, for type 2 diabetes mellitus
- The agreement gave Sanofi the option to terminate the deal in the event the proposed clinical trials failed
- Sanofi then initiated several studies investigating the efficacy and safety of Sotagliflozin to lower HbA1c levels in patients with type 2 DM and severe CKD
- They also initiated 2 large scale prospective double blind randomized studies of Sotagliflozin in patients with type 2 DM

Academic-Industry Relations My Experience with Sanofi-Lexicon (THE BAD)

- The SOLOIST trial-Evaluation of Patients with type 2 DM and Heart Failure (n=4000, 3000, with HFrEF and 1000 with HFpEF – Randomized at the time of transition from iv diurtetics to oral therapy after an episode of hospitalization for worsening HF to test the effectiveness of Sotagliflozin to reduce CV mortality and hospitlizations for HF
- The SCORED trial-Evaluation of patients with type 2 DM and CKD (n=9000) to test the effectiveness of Sotagliflozin to prevent the development and progression of end stage renal disease (ESRD)

Academic-Industry Relations
My Experience with Sanofi-Lexicon (THE BAD)

- On July 25th 2019 Lexicon received notice that Sanofi was terminating their agreement with Lexicon to develop Sotagliflozin in patients with type 2 DM
- Sanofi stated that the reduction in HbA1c levels in patients with severe CKD and DM was not sufficient to justify further clinical development
- This claim was subsequently disputed by Lexicon
- At the time of the termination notice approximately 8000 patients had been randomized into the SCORED trial and 1000 into the SIOLOIST trial
- The future conduct of these trials became uncertain since Lexicon is a small biotechnology company and did not have the resources to continue the trials
- On learning of the termination of the Sanofi-Lexicon agreement to terminate the clinical development of Sotagliflozin for type 2 DM in patients with CKD and HF the executive committee of the SCORED and SOLOIST trials initiated a series of conversations with the senior management of Sanofi and Lexicon pointing out that in our opinion it was unethical to terminate these 2 large scale trials since patients had entered these trials in good faith knowing that they might be randomized to placebo-but were willing to do so for the public good.

Academic-Industry Relations
My Experience with Sanofi-Lexicon (The Bad)

- Premature termination of the trials due to economic considerations without providing an answer to the question of whether Sotagliflozin was effective and safe we believed was unethical
- On September 11th 2019 Sanofi and Lexicon reached an agreement. Sanofi would pay Lexicon $260 million to exit the agreement. 80% of the fee will be paid upfront and 20% of the remaining amount split between 2 installments, payable within 6 and 12 months of the settlement
- During the transition period Sanofi will continue to run the SCORED and SOLOIST trials with advice from Lexicon.
- However, the $260 million settlement fee paid to Lexicon is insufficient to complete the trials
- Lexicon is currently seeking a partner to continue the 2 trials
- The ultimate fate of the trials is uncertain at this time-thus the ethical dilemma remains.

Academic-Industry Relations
My Experience with the NLBI

The GOOD

- Chairman of the Steering committee of the NHLBI TOPCAT trial (Evaluation of spironolactone vs placebo to reduce CV mortality and hospitalizations for patients with HFpEF (n=3200).
- Co-chairman of the steering committee of the Swedish Heart foundation/NHLBI SPIRRIT trial (Evaluation of the role of spironolactone on CV mortality and CV hospitalizations in patients with HFpEf (n=3600))

These trials allow the evaluation of generic drugs that would not be funded by industry and could provide results that change clinical practice, reduce CV mortality, CV hospitalizations and health care costs. Government and academically funded trials are perceived by the public as being less biased and objective than industry funded trials.

Academic-Industry Relations
My Experience with the NHLBI

- The BAD
- In comparison to pharmaceutical industry funded trials the reimbursement per patient in NHLBI and publically funded sponsored trials is relatively low
- In TOPCAT the relative underfunding led to the selection of clinical sites in Russia and the Republic of Georgia many of which did not have prior experience in recruiting patients for HF trials. As a result patients recruited from Russia and the Republic of Georgia did not have a placebo event compatible with epidemiologic and prior randomized trials of patients with HFpEF in comparison to those recruited from the Americas who did have a placebo event rate compatible with prior studies. Furthermore many of the patients assigned to spironolactone and who stated that they were taking the study drug assigned in Russia and the Republic of Georgia did not have detectable metabolites of spironolactone.
- The SPIRRIT and TRANSFORM trials are ongoing with approximately 1000 into each trial.
- However, both SPIRRIT and TRANSFORM are open label pragmatic trials with a relatively low per patient reimbursement rate
- While pragmatic open label trials often have less inclusion restrictions then standard blinded randomized trials and therefore may better reflect" real world" conditions they also increase the risk of crossovers thereby making it more difficult to provide a clear answer to the question being asked.

Academic-Industry Relations
A Cardiovascular Clinical Trialists PERSONAL PERSPECTIVES and Reflections

(The GOOD and The BAD)

Summary/Conclusions

- Both industry and NHLBI or publically funded cardiovascular clinical trials are important to further reduce CV mortality and hospitalizations and thus health care costs.
- Both industry and NHLBI or publically funded cardiovascular clinical trials pose potential problems
- Industry sponsored clinical trials may raise ethical and conflict of interest issues while NHLBI or publically funded trials often suffer from inadequate funding and or implementation