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# Challenges to Industry in the Development of Pharmacological Therapies for the Treatment of Alcohol Abuse and Dependence

# Disclosures and Disclaimers

- Joseph Palumbo is a full-time employee of Johnson & Johnson Pharmaceutical R&D, LLC
- Johnson & Johnson has no marketed products which are approved for the treatment of alcoholism
- A member of his immediate family is employed by Actelion
- Dr. Palumbo is a member of the Adjunct Faculty at Yale University.
- He has no conflicts of interest related to Yale University regarding academic advancement, grant support or competition, intellectual property, or to discoveries or invention rights
- All comments and opinions expressed are solely those of Dr. Palumbo, except as otherwise cited, and should in no way be construed as representing the opinion or position of either Johnson & Johnson Pharmaceutical Research and Development or Yale University

# Objectives of this talk: My opinions

- ACTIVE has been successful in reducing the perception of development risk in alcohol use disorders to its industry participants
- ACTIVE has been successful in opening up the beginnings of true cooperation in the pre-competitive space
- ACTIVE has created a non-adversarial and respectful forum among scientists (academic, regulatory, federal, pharma) to collaboratively advance the science and treatment of alcohol use disorders
- The current economic models do not foster the kind of rigorous large scale research in this area that is required for transformational change
- There is a necessity for focus on validation of precise translational models through rigorous hypothesis testing
- Risk can be predicted and reduced, but not eliminated
- The willingness to take on risk should be rewarded with the creation of value
- Nonetheless, given the perceived risks, incentives will likely be necessary to jump start larger industry initiatives in alcohol and addictions
- Barriers to cooperation in the R&D space are multilateral; ACTIVE has helped to define and to begin to diminish those scientific impediments in the greater service of the public health
- Primary care is about to see the model of care for alcohol related disorders change drastically, and to become both medicalized and reimbursed. These physicians need our help and expertise to best manage this population.

# The Parable of the Flying Car

- Flying cars are here – but you may not be seeing one in your driveway very soon
- The investment community sees the risk:
  - Each vehicle will cost too much
  - Will need special runways
  - Will need special regulations
  - No current infrastructure
  - Too many variables, and too long to see a return on investment
  - Would prefer immediate high return with little risk
- Would they have greeted the automobile (the Interstate System) or the airplane (International Airports) in the same way? Would they have failed to invest?
- Anything novel is less predictable, requires energy and investment, and considerable risk.
  - Not a big deal for widgets, but a huge issue for your "only child" in a time of limited resources. (Your Mutual Fund depends on this.)
- Hence, the explanation for the Parable of the Flying Car. (It's not the 50's anymore.)

**So, no flying car… *but, why no new mechanisms marketed for the treatment of Alcohol related disorders?***

**Sure, what we've got works, but, come on now!**

- Is it lack of innovation?
- Is it lack of novel targets and mechanisms?
- Is it confusion regarding regulations?
- Is it an excess of black bile?
- There must be an explanation, isn't there?
- For the development of therapies to treat alcohol related conditions, **context is everything**

# Motivations vary

- Consider the source of funding and what is expected as productivity in return for the grant or investment
- Academic
- Biotech and Small Pharma
- Large Pharma
- All play very different roles
- ***The following slides represent a rapid assessment of the playing field***

# Academic research

- **Academic** research is funded by "gifts", and rewards are promotion, lab space, tenure (hence, my disclaimer)
  - Are driven to identify targets, mechanisms, validity in non-human species
  - Clinical relevance and magnitude of effect are not always primary
  - Typically rely on pharma for agents with which to perform clinical research. Studies are typically small.
  - *Produce knowledge and generate hypothesis*
  - *Customers are Nature, Science, Cell, NIMH and other funding sources*

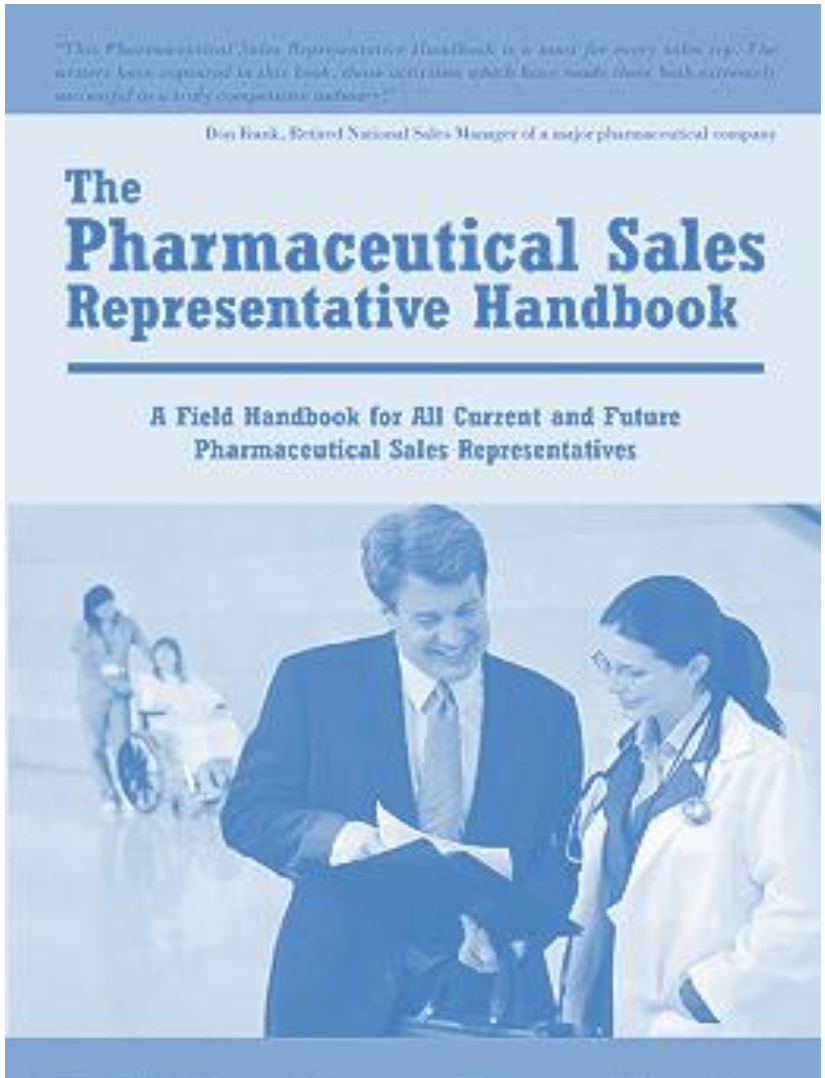
# Small companies and biotech

- **Small** companies funded by investors
  - Will take on reasoned risk for large return; increasingly up to the 100 million to 1 BN range when successful
  - Do not typically invest in real interrogation of the drug, or its mechanism, or its clinical relevance unless business critical to do so
  - Not necessarily motivated to look for warts
  - Not necessarily centered on science or hypothesis testing
  - *Produce value by conducting high risk early research*
  - *Customers are investors and bigger companies with permanence*

# Larger companies

- **Big** companies seek stability and growth …
  - Ultimately, may often have remarkably little data upon which to make a decision regarding investment and development – must typically accept compounds still at rather high risk, or lose potential opportunity to competitors
  - Lost opportunity costs must be considered
  - Tend to treat accepted medical conditions, not target behaviors as related to commercial and regulatory approval concerns
  - *Produce medicines*
  - *Customers are regulatory bodies and physicians*

# If one is planning to market a pharmaceutical, what does one want?




- Low development risk (but, no "me too" drugs allowed)
- Ability to create a business and remain invested over years (closing down a company is expensive)
- Ability to find the customers
- Customers happy with clinical efficacy and safety (enable the MD to be a better doctor)
- Adequate reimbursement
- Ability to re-invest in research and personnel
- Create a cycle of repeated success

# How does this look for alcohol use disorders?

# To progress, all of these stars must align

- Pre-clinical view
  - Which mechanisms, which targets, which systems
- Translational view
  - Which animal screens best predict human clinical response
  - Best methodologies may involve creating dependence with models for reinstatement – very complex, very expensive, very time consuming, may be a dying art
- Clinical view
  - Active drinking?
  - Prevention of recurrence?
  - Which target symptoms of alcohol use?
    - Dependence?
    - Heavy use?
    - Binge use?
    - Withdrawal?
    - Craving?
    - Biomarkers?
    - Organ system and harm reduction measures other than ethanol consumption?
    - Measures of function and quality of life?
    - Designs for US? Designs for EU? Designs for ROW?

# And how about aligning these stars, too?

- Commercial view
  - Who are my customers? Are they satisfied with what they have? Do they want or need what I have?
  - Can I make a fair profit to reinvest?
- Regulatory view
  - What guidance do I have? Is it globally consistent?
- Scientific leadership
  - Does this appeal to me? Would I rather cure bipolar disorder? What is the technical likelihood of success vs. another program?
- Global experts
  - Is this consistent with my hypotheses and research interests? Can I afford the stigma of working with pharma?
- 3rd party payers
  - I don't want to pay for anything that is not proven to be better than currently available therapies, and if I do pay, the new intervention has to save me money

# The Public and investors

- Consumers
  - How certain am I that if I take this, and pay out of pocket, that I will actually get well? How likely is this to hurt me?
  - How influenced am I by family, my sponsor, Tom Cruise, "Black Boxes", Political agendas, etc?

- Investment community
  - How smart an idea is this?
  - How many quarters does it take for me to multiply my investment?
  - Cash is cash right now… an investment is a risk
  - In business for a return, not in business to advance science, The process is a vehicle for the growth of wealth

# Perception of the clinical challenges: Myths and reality

## Perceptions

- Patient population highly unreliable
  - Less desirable patients for inclusion in clinical trials
    - Real and perceived character types
      - Vanishingly small number of "pure" alcoholics for hypothesis testing
      - High percentage of antisocial personality traits
      - Less likely to have stable home address, employment, or family
      - High likelihood of being lost to follow-up
      - High proportions of missing data
    - Biology
      - Multiple medical risks and disorders, few of which may be disclosed
    - Unreliable subjective responses
      - Placebo responses historically similar in magnitude and effect sizes to standard therapies
  - Reliance on recruitment methods driven by economics of reward
    - No historical record
    - Incentives are questionable on several levels
  - These perceptions may be driven by the experience of urban and inner city based research, as well as the use of less experienced clinical trial sites

## Reality

- **Experienced researchers can easily recruit "pure alcoholics"** who respond to ads – there is a highly prevalent population of individuals who are not motivated to attend programs at designated substance abuse treatment programs in the form in which they currently exist
- "Clinical populations" who self refer, or who are referred by law enforcement, most likely do not represent the larger population of individuals who suffer from alcohol use disorders.
  - However, this highly visible "tip of the pyramid" does have more dual diagnosis, drug abuse, and may be antisocial.
- A focus on diagnosis and treatment within the familiar confines of primary care makes sense in order to address the public health needs of this larger population.
  - This is exactly what the current health care proposals advocated by the current administration intend to accomplish
- In the COMBINE Study, this experienced group suffered **only 5% of people lost to follow-up and missing data!**
- Nearly all of us are familiar with the challenges of recruitment and management in clinical trials for major depression,
- ***Although there is a perception that it is difficult to do perform studies in the treatment of alcohol use disorders, experts who have worked in both fields state that: in reality for experienced researchers, alcohol research is much less problematic***

# Getting to the patients: If we build it, will they come?

**Conventional Wisdom:**

Culture of care is perceived by marketing management as forbidding and commercial model to be daunting

- Not sure who the customers are
  - Alcoholism not managed clinically by MDs
    - Hostile to medical/ pharmacologic interventions
    - Never substitute a drug for a drug
  - Alternate system of care means that an exceptional investment must be made to create a new form of organization that can reach "point of care", or must rely on psychiatrists (few who embrace addictions treatment), or reach and educate primary care physicians who are taught to disregard pharmaceutical educational efforts
    - Regardless, must be reliant on the interventions of primary care physicians, who may see symptoms rather than syndrome
  - Reimbursement for intervention is very questionable – what code, what diagnosis, what procedure, which carve out – MDs do not want to lose money
  - Academic, Governmental, and Advocacy opinion leaders unaligned, no attractive "poster child" for the disorder
  - DSM-V to have no medical markers or complications of disease, making typical medical algorithmic practice unlikely to generate alcohol related diagnoses in the absence of self report

**The New Reality: Can we handle the truth? The environment is evolving!**

- Today, Bob Swift and others have shown that most AA groups actually see medication as neutral or positive
- The Affordable Health Care Act and Parity Legislation is about to change everything. Alcohol Use Disorders will be treated in full equity to chronic conditions such as Diabetes Type 2. Billing codes, procedures, and interventions which have not be available, or which could not be incorporated into Primary Care will now be available for full reimbursement.
- The markers of alcohol consumption and heavy drinking may not have been yet incorporated into DSM V , as it now stands, but these measures will be readily available to Primary Care clinicians to guide their interventions

# Convincing the decision makers to write a big check: Few analogs of prior medical and marketplace wins

- Less certain that there can be a cycle of success if one has not been seen before in the same place (this thinking favors "me too" agents, which 3rd party payers abhor)
  - Perception that prior experimental agents that have run into major turbulence and have never landed without damage
  - Perception that each marketed agent has struggled with acceptance or adverse events
  - Fear that drugs that modulate craving and reward will cause amotivational syndromes, and be interpreted as being causal of dysphoria and/or suicidality (i.e. generate losses through litigation)
  - Fear of loss, rather than gain – akin to drug treatments for obesity or for women's reproductive health
  - (Parenthetically, you all have colleagues making millions working for the plaintiff's bar while you post your hourly consulting fees from working with start-ups…)

# ACTIVE has worked to reduce the perception of risk to industry

- Address joint technical and design challenges in the pre-competitive space
- Clear the mythology around regulatory pathways
- Address the question as to whether or not reductions in alcohol consumption, as determined by heavy drinking days, is linked to better patient outcomes and quality of life
- Provide guidance for handling the challenges of the studied population, including methodologies for missing data
- Address issues of trial design for both induction of reduction and its maintenance
- Provide an educational and learning forum
- Sharing of perspectives from recognized leaders in academia, government, and industry
- Reduction of perceived risk
- Enhanced likelihood of technical and regulatory success

What more is there to solve?

# Debunk today's mythology

# Responsibility: The unified scientific community

- Abandon the concept that one can innovate without risk
  - *Little known fact:*
    - The pre-clinical science is particularly powerful in terms of prediction of effect in addiction versus that observed in cognition, mood, and most neurologic conditions (save epilepsy)
  - *Treatment of alcoholism and addictions may be able to allow pharma to return to a cycle of success – **if** the drug is what consumers actually want*
    - *The public health need is enormously compelling*
    - *Investment and scientifically driven transparency can go a long way to restoring the industry to a credible and trusted status*
- Academic scientists must advocate and support novel and innovative research within Pharma, and need to be free of any personal bias that may be generated by their own hypotheses or funding sources

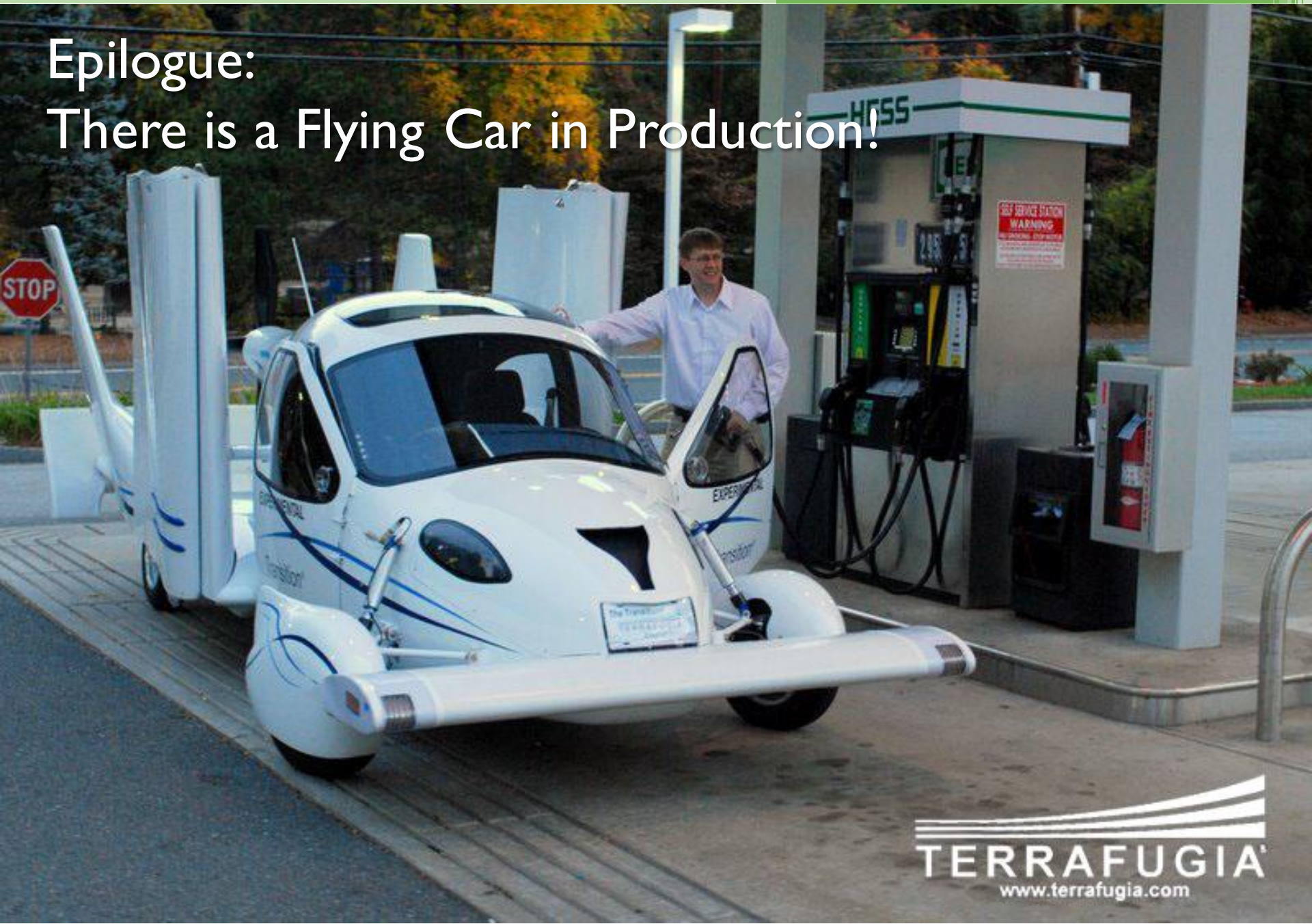
# Translation, translation, translation…

- Biotech and small pharma are not well poised to provide rigorous and necessary translation (the economic models do not support it).
- Biomarker development ,as a means to support rigor in translation, needs to be an utmost priority if we seek to remain a viable area for industry research
- Big Pharma assumes great risk at great cost, but likes to skip translation, doing so at its own peril
  - In this target population, if the agent does not have at least a moderate effect size (similar to SSRIs, neuroleptics, antihypertensives), the utility in clinical care will be questioned and possibly rejected
- To wit – the current economic models do not foster the kind of rigorous large scale investment and research in this area that is required to advance the public health
- If I were king :
  - NIH/ NIDA/ NIAAA to move very aggressively into translation;
  - Reward innovation in this area in the way that we have recognized orphan indications and pediatric development
  - Protect patents and the integrity of labels
  - Allow transparent reward of individuals and institutions, regardless of employer, for important contributions to the public health
  - No one should be discouraged from advancing true innovation in medicine for fear of modern McCarthyism

# Take home messages

- ACTIVE has been successful in reducing the perception of development risk in its industry participants
- The current economic models do not foster the kind of rigorous large scale research in this area that is required for transformational change
- Getting there is all about hypothesis testing, scientific rigor and a truly focused emphasis on translation
- Risk can be predicted and reduced, but not eliminated… the willingness to take on risk is rewarded with the acknowledgment of creation of value
- Incentives will likely be necessary to jump start larger industry initiatives in alcohol and addictions
- Barriers to cooperation in the R&D space are multilateral; ACTIVE has helped to define and to begin to diminish those scientific impediments in the greater service of the public health
- Primary care is about to see the model of care for alcohol related disorders change drastically, and to become both medicalized and reimbursed. These physicians need our help and expertise to best manage this population.

# Epilogue:
# There is a Flying Car in Production!



# Questions?