Collaborating with Academia

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Rare Bootcamp
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TEXAS A&M UNIVERSITY

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Disclaimer

My opinions are based on my experiences and perspective.

I use a cynical tactic to illustrate the nuances — albeit factual — of collaborating with academic researchers.

Every investigator, department, and institution is different.

My Background

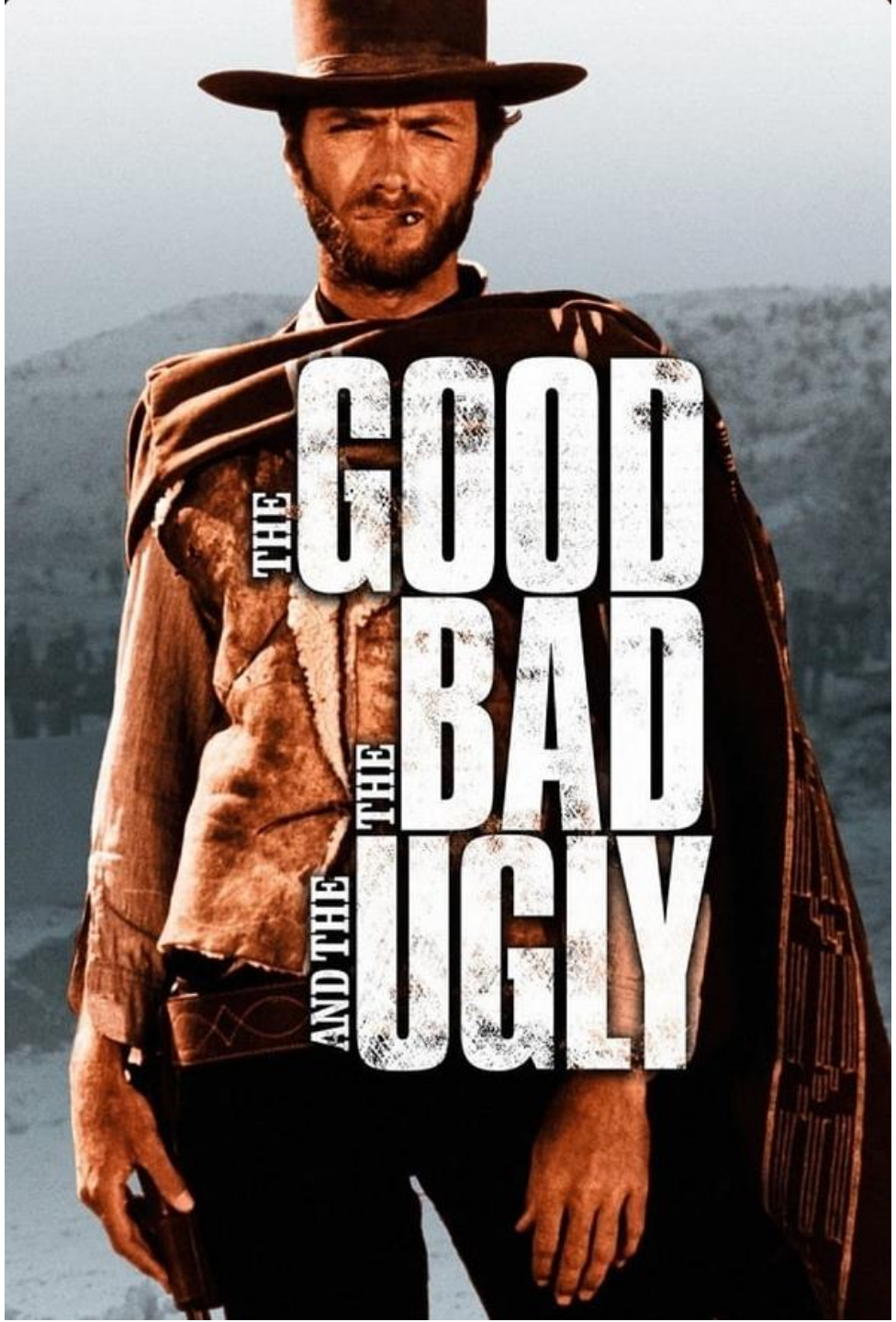
- Tenured Professor, Texas A&M University (2008-present)
- Chief Scientific Officer, GeneTx Biotherapeutics (2017-2020)
- Executive Director Molecular Genetics, Ultragenyx Pharmaceutical (2020-present)

My Background

- Continuous funding from federal agencies, foundations, companies, and licensing agreements.

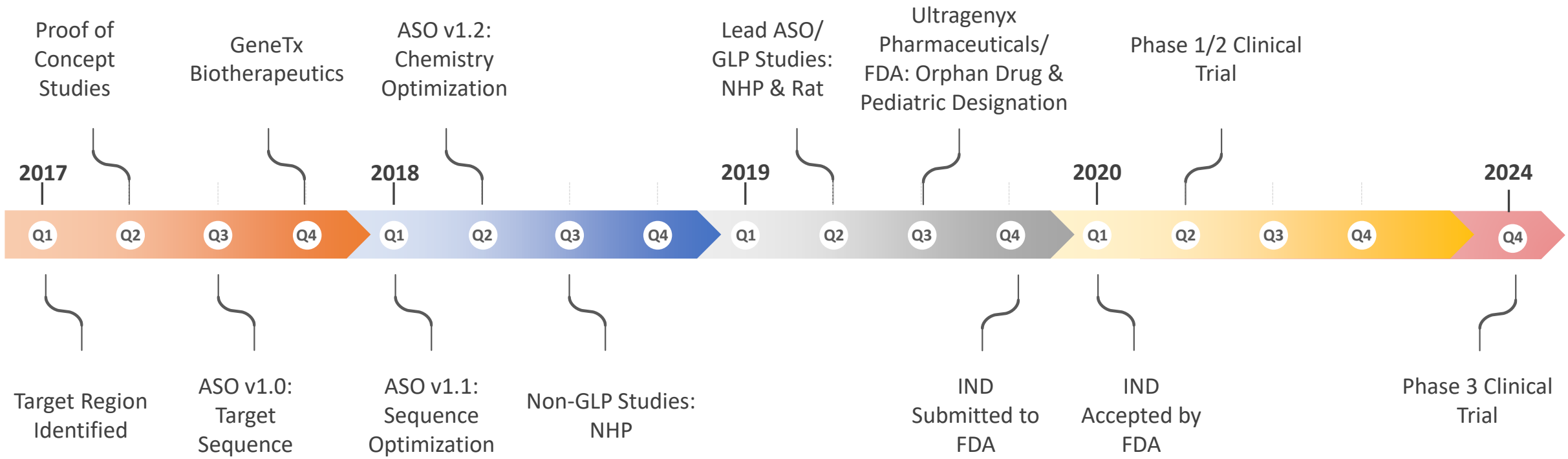
- 15 years collaborating with rare disease foundations.

Collaborating with Academia



The GOOD

The First Molecular Therapy for Angelman Syndrome to Advance into Clinical Development



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THE TEXAS A&M UNIVERSITY SYSTEM

TEXAS A&M AGRILIFE RESEARCH

genetx

ultragenyx

the BAD and the UGLY

Academic Research

The largest flea markets in the world

Academic Research

The currency of our trade is measured in grant dollars and publications

NIH National Institutes of Health
Turning Discovery Into Health

Human Molecular Genetics, 2008, Vol. 17, No. 1 **111–118**
doi:10.1093/hmg/ddm288
Advance Access published on October 16, 2007

The Angelman syndrome ubiquitin ligase localizes to the synapse and nucleus, and maternal deficiency results in abnormal dendritic spine morphology

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Loss of function of the maternally inherited allele for the *UBE3A* ubiquitin ligase gene causes Angelman syndrome (AS), which is characterized by severe neurological impairment and motor dysfunction. In addition, *UBE3A* lies within chromosome 15q11–q13 region, where maternal, but not paternal, duplications cause autism. The *UBE3A* gene product, E6-AP, has been shown to function both as an E3 ligase in the ubiquitin proteasome pathway and as a transcriptional coactivator. However, the specific role of E6-AP in the brain, or how loss of function of E6-AP results in AS, is unclear. Herein, we show, using a recombinant transgenic mouse expressing a *Ube3a*^{YFP} fusion gene, that the maternal *Ube3a*^{YFP} allele is upregulated and preferentially expressed in neurons, and that the fusion protein, E6-AP:YFP, is enriched in the nucleus and dendrites *in vivo*. We also show that E6-AP:YFP localizes to the nucleus and to presynaptic and postsynaptic compartments in cultured hippocampal neurons. Furthermore, we show that cerebellar Purkinje cell number and dendritic branching are not affected in *Ube3a* maternal-deficient mice, but that dendritic spine development, including spine morphology, number and length, is affected on cerebellar Purkinje cells and on pyramidal neurons in the hippocampus and cortex. Collectively, these data suggest that the neurological deficits observed in AS patients and in AS mice may result from specific abnormalities in synaptic development and/or plasticity.

INTRODUCTION

Angelman syndrome (AS) is characterized by severe mental retardation, absence of speech, ataxia and a happy disposition (1,2). The AS gene, *UBE3A*, encodes the E6-AP ubiquitin ligase and is subject to genomic imprinting, with preferential maternal-specific expression in brain and, more specifically, in neurons but not in glia (3,4). Maternal but not paternal interstitial duplications of chromosome 15q11–q13 cause autism (5). These duplications encompass multiple genes, but *UBE3A* is a strong candidate to contribute to the autism phenotype in 15q11–q13 duplication cases based on its imprinted status and known causative role in AS (6). Autism spectrum disorders are seen with Prader–Willi syndrome and AS, the two phenotypes associated with paternal and maternal deletions of 15q11–q13, respectively (7,8).

Mice with a maternal null mutation in *Ube3a* (AS mice) have defects in long-term potentiation (LTP) and manifest motor and behavioral abnormalities that parallel findings in AS in spite of normal cellular architecture in the brain (9). The neurological deficits in AS mice have been directly linked to the postsynaptic calcium/calmodulin kinase type 2 (CaMKII) signaling pathway, as AS mice have increased inhibitory phosphorylation of αCaMKII in the brain (10). Moreover, the learning and behavioral deficits present in AS mice can be rescued through a mutation in CaMKII that prevents its inhibitory phosphorylation (11). Other reports have linked E6-AP to various neurologically relevant proteins including epithelial cell-transforming sequence 2 oncogene (Ect2) (12), neuronal protein interacting specifically with TC10 (nPIST) (13) and myc-binding protein-2 (MYCBP2)

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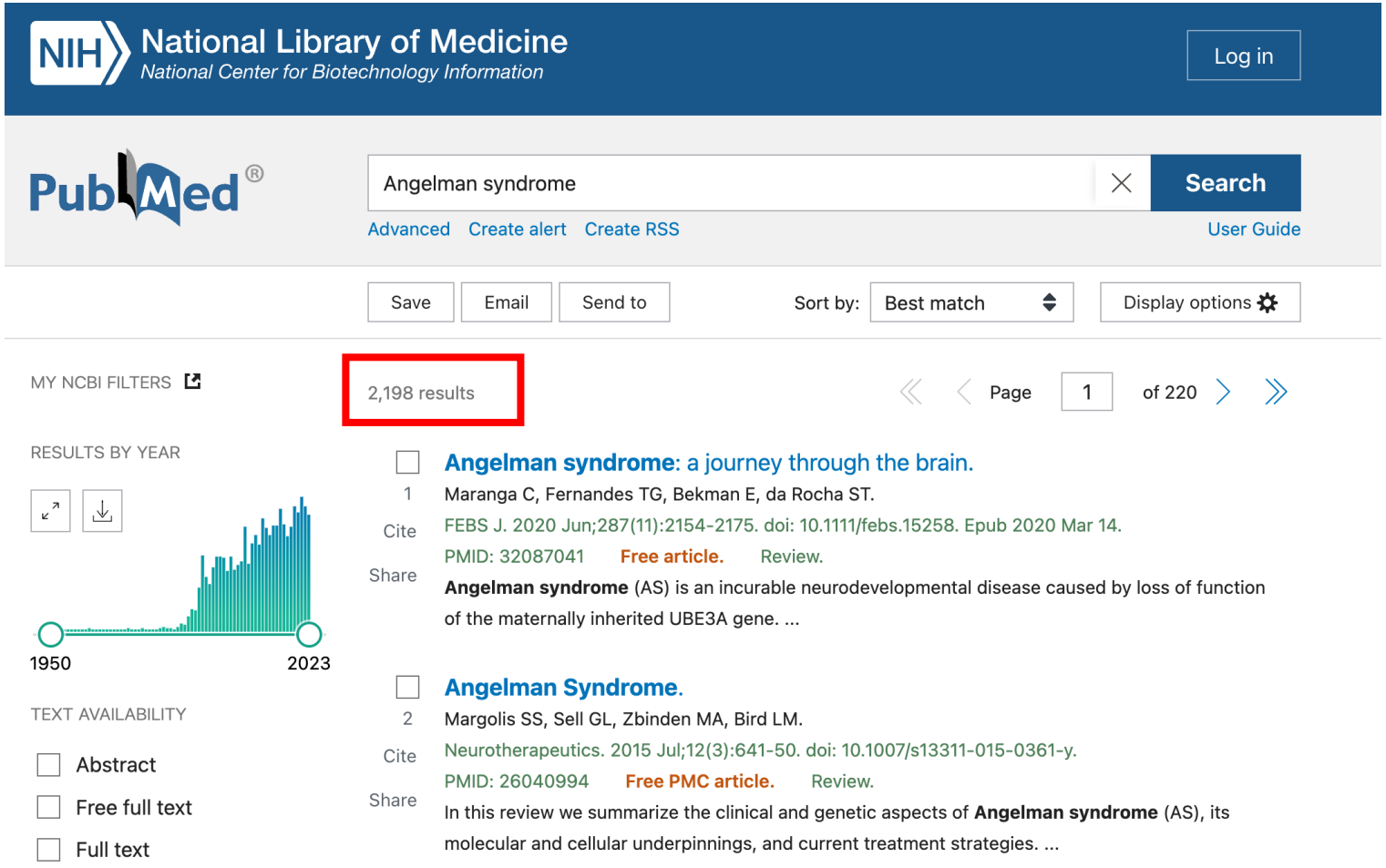
Scientific Articles

There are too many of them, and most of them are wrong or biased



A PROPOSED STRUCTURE FOR THE NUCLEIC ACIDS

By Linus Pauling and Robert B. Corey

Gates and Crellin Laboratories of Chemistry,* California Institute of Technology

Communicated December 31, 1952

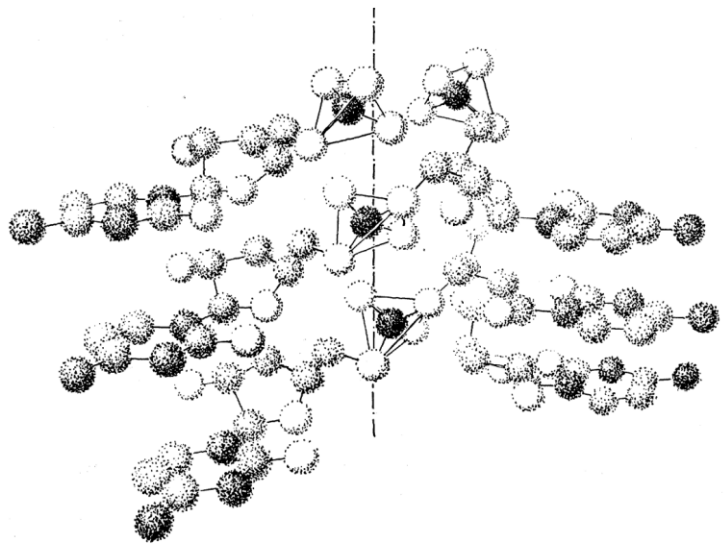


FIGURE 4

Perspective drawing of a portion of the nucleic acid structure, showing the phosphate tetrahedra near the axis of the molecule, the β-D-ribofuranose rings connecting the tetrahedra into chains, and the attached purine and pyrimidine rings (represented as purine rings in this drawing). The molecule is inverted with respect to the coordinates given in table 1.

› Proc Natl Acad Sci U S A. 1953 Feb;39(2):84-97. doi: 10.1073/pnas.39.2.84.

A Proposed Structure For The Nucleic Acids

L Pauling [1], R B Corey

Affiliations + expand

PMID: 16578429 PMCID: PMC1063734 DOI: 10.1073/pnas.39.2.84

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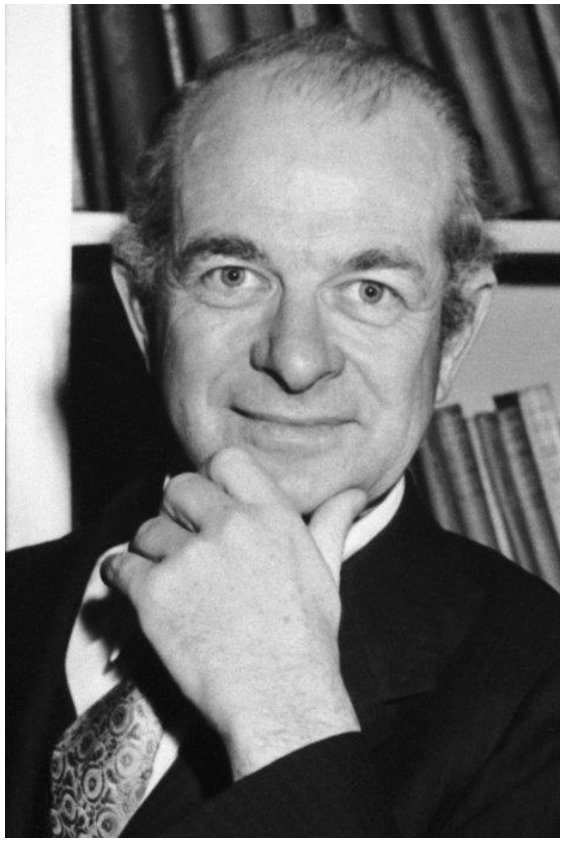
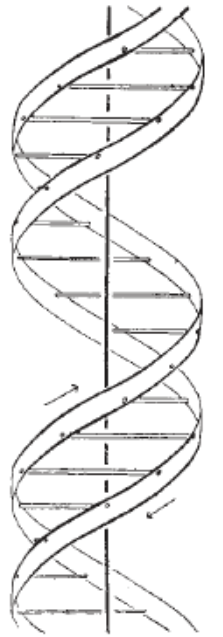


Linus Carl Pauling

Nobel Peace Prize 1954 and 1962

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid



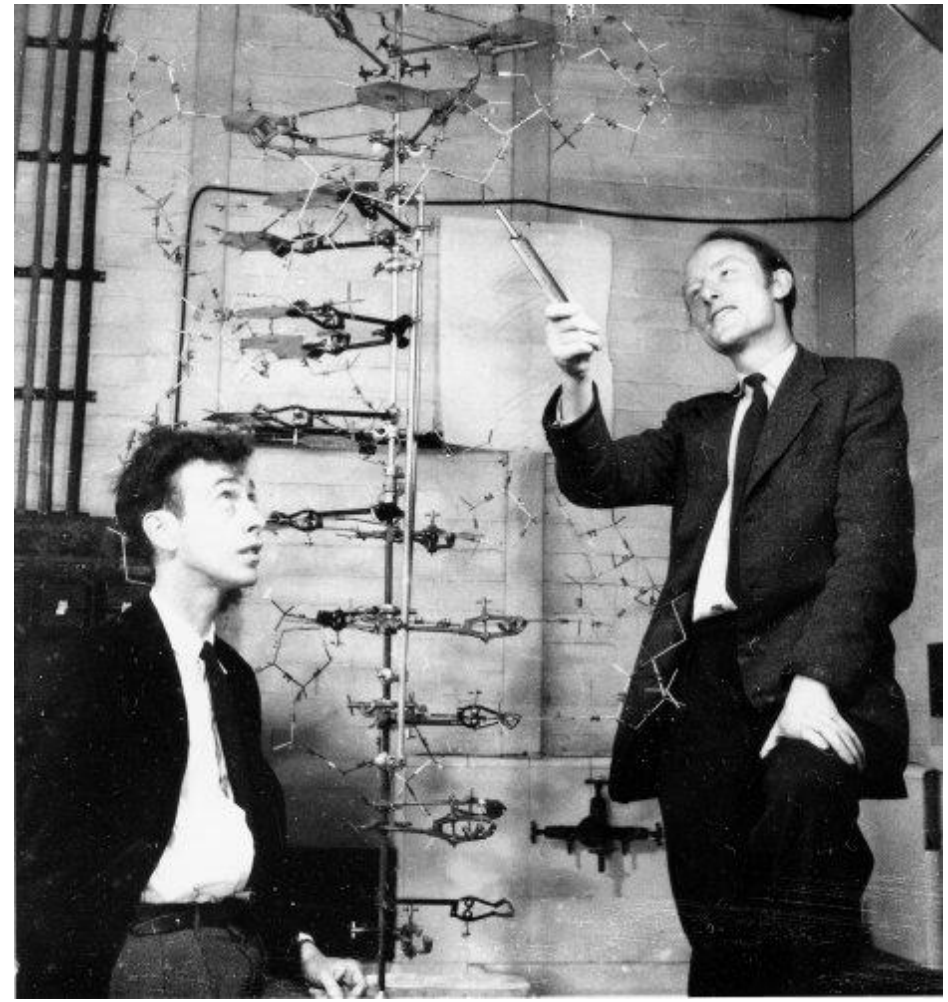
This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

› Nature. 1953 Apr 25;171(4356):737-8. doi: 10.1038/171737a0.

Molecular structure of nucleic acids; a structure for deoxyribose nucleic acid

J D WATSON, F H CRICK

PMID: 13054692 DOI: 10.1038/171737a0

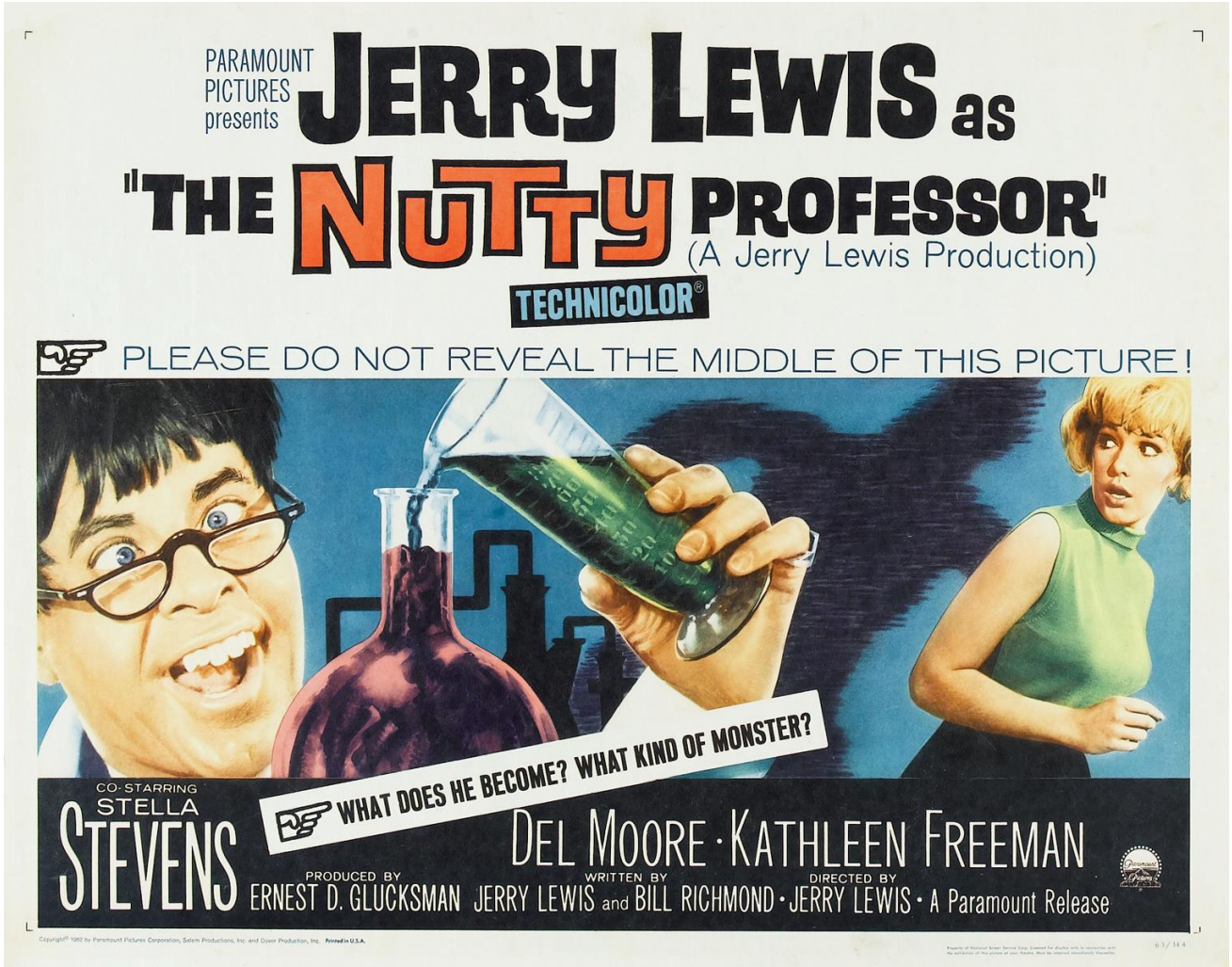


James Watson and Francis Crick

Nobel Peace Prize 1962

Academic Research

An unusual business model involving the most unusual people

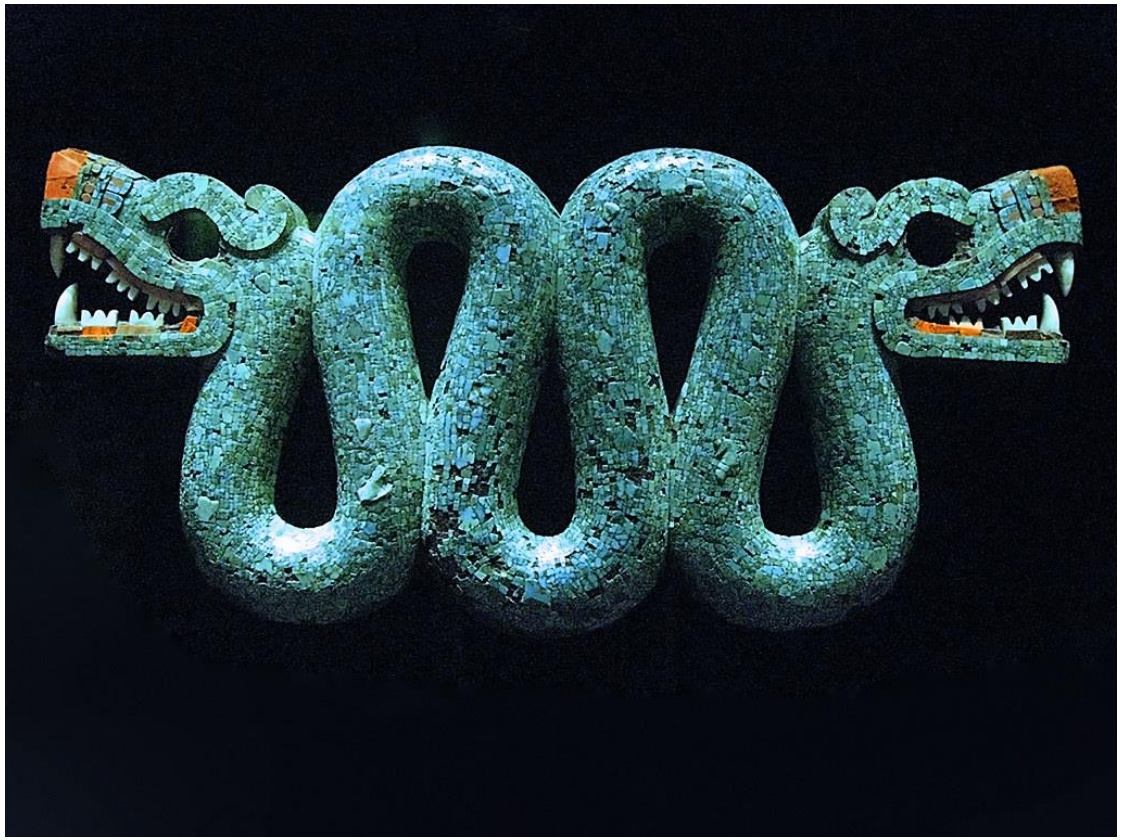


Academic Collaborators

One collaborator is many partners with different priorities

Principal Investigator Priorities
- Tenure and Promotion
- Solvency
- Trainees

Other priorities
- Teaching
- Lab/personnel situations
- Risk
- Competition

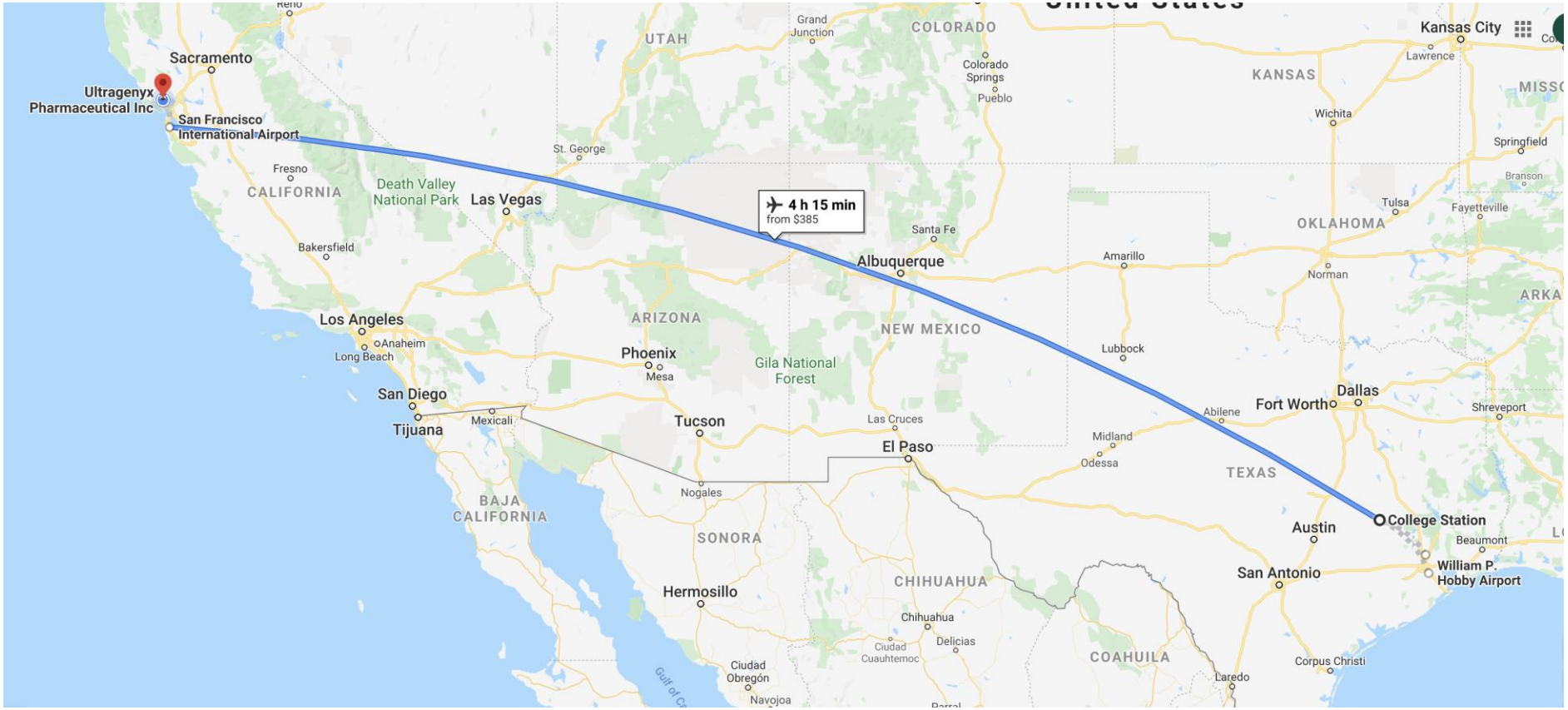


Institutional Priorities
- Academic freedom
- Protecting faculty and trainees
- Intellectual property

Other priorities
- Business model
- National status
- Politics
- Internal initiatives

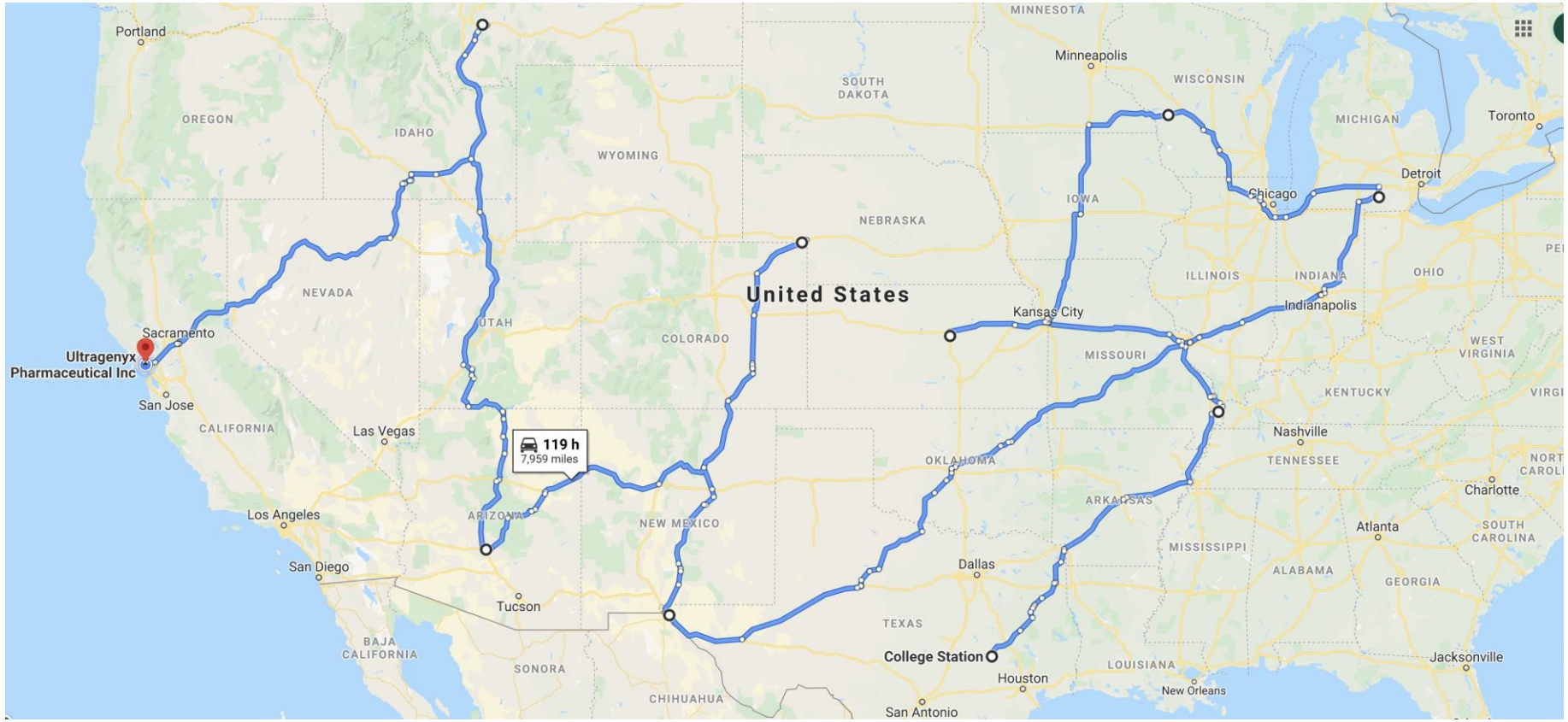
Your Journey with an Academic Collaborator

Expectation



Your Journey with an Academic Collaborator

Reality



Conclusions

- Academic research is the engine that drives innovation, but it is a unique and often misunderstood ecosystem - try to understand it.
- Find a collaborator who understands your objectives and timelines, and try to understand their objectives and timelines – every person and situation is different.
- Trust your academic collaborator, but do not make assumptions about their situation, environment, institution, etc. – find out as much as you can as early as possible.
- Be dubious about scientific publications, scientific claims, timelines, etc. — it is the nature of research to embellish and overpromise.
- Be focused, but expect twists and turns and failures and frustrations — they are inevitable.

Thank you!

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