

The Jagged Line: *Why the Best Careers Never Run Straight*

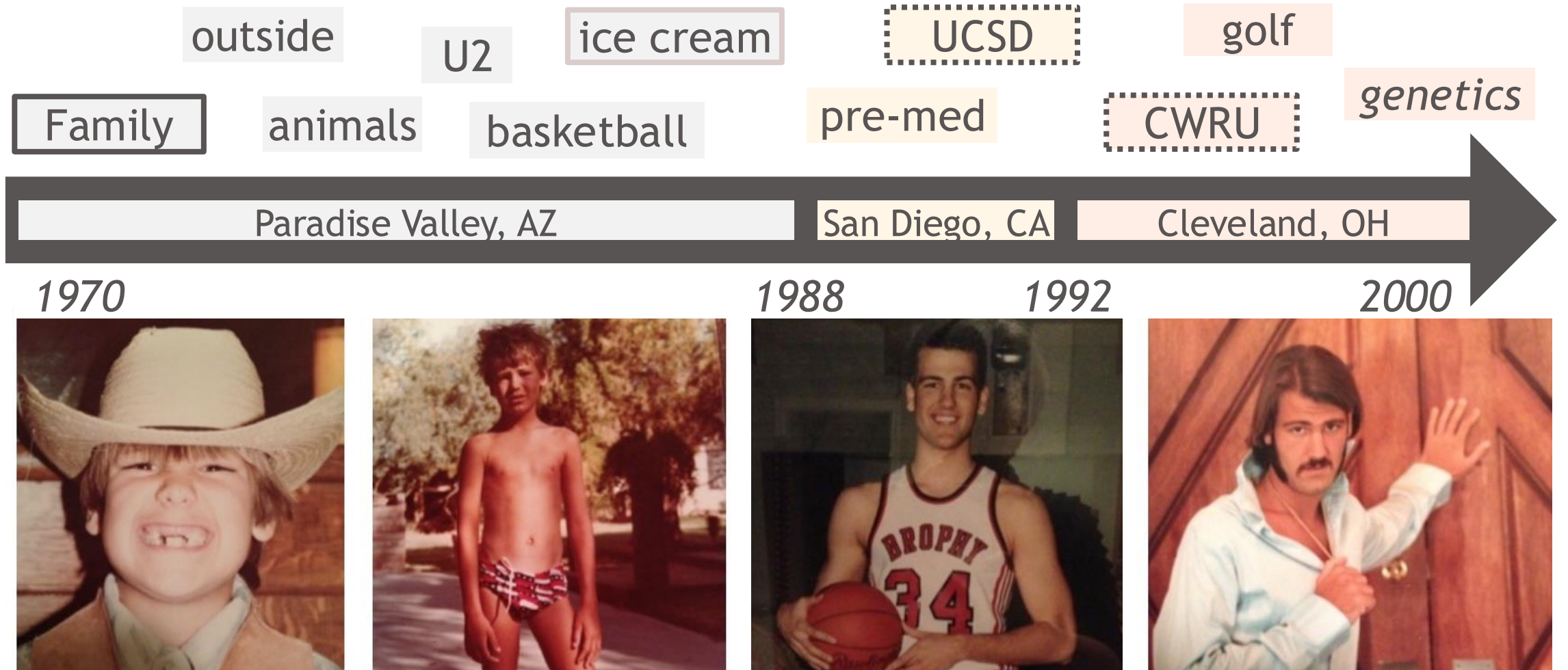
Robert Plenge
April 9, 2026

*Yale Biotech Club (YBC)
2026 Life Sciences Career Fair*

Agenda

- **My experiences - and lessons learned**
 - Beware of the “personal narrative”
 - Challenge your assumptions
 - Be curious, be courageous, and go deep
 - Ask big questions - manifestly important, nearly impossible
 - Embrace a jagged line in career development
- **What's next**
 - End-to-end R&D principles
 - Functional cures in autoimmunity
 - Artificial Intelligence (AI)

My early years



Beware of the personal narrative

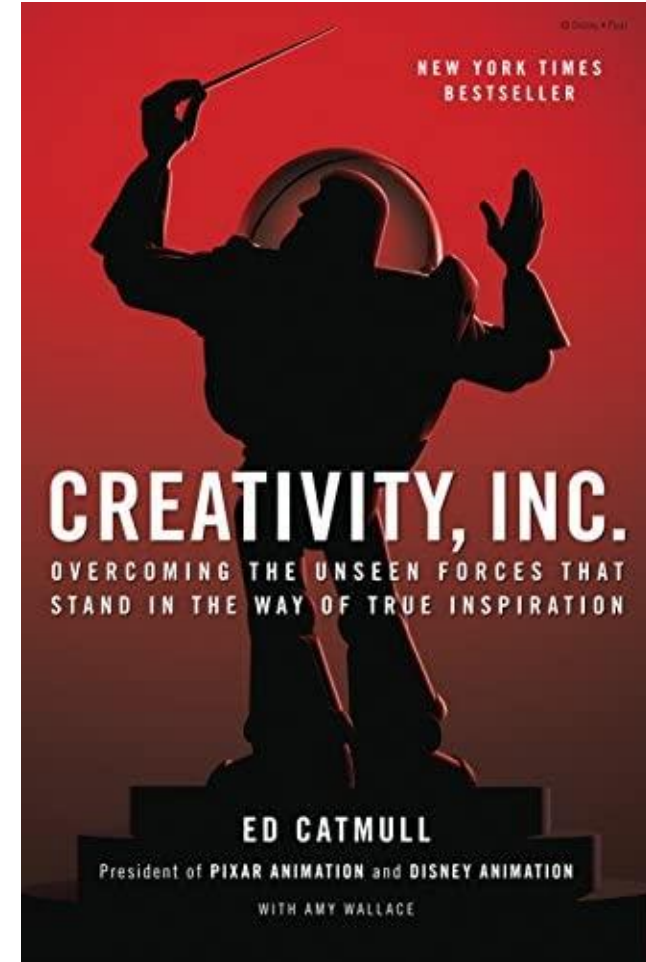


- Get advice for YOU.
- What does it mean for YOU in your world view?
- What does it mean for YOU in the context of what you're going through?

<https://www.plengegen.com/blog/failure/>

<https://www.plengegen.com/blog/advice-younger-self/>

Beware of the personal narrative



<https://www.plengegen.com/blog/failure/>

<https://www.plengegen.com/blog/advice-younger-self/>

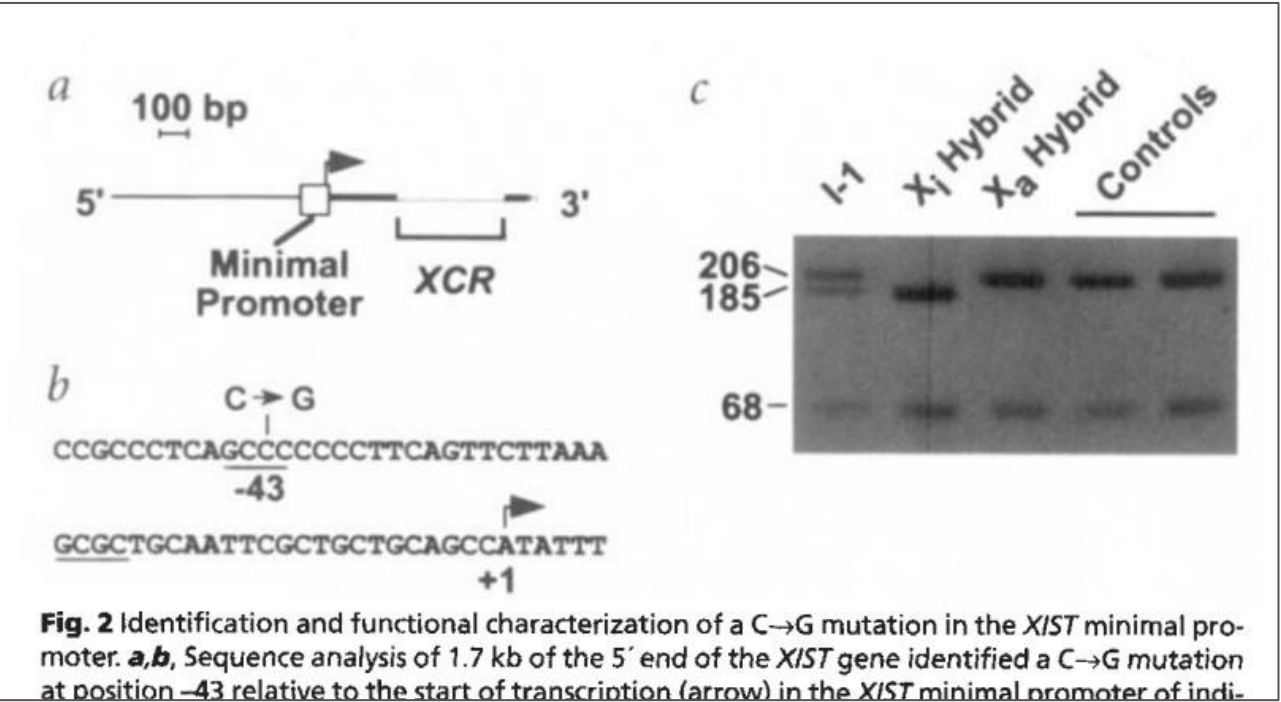
My PhD years - a discovery & people that changed my career

© 1997 Nature Publishing Group <http://www.nature.com/naturegenetics>

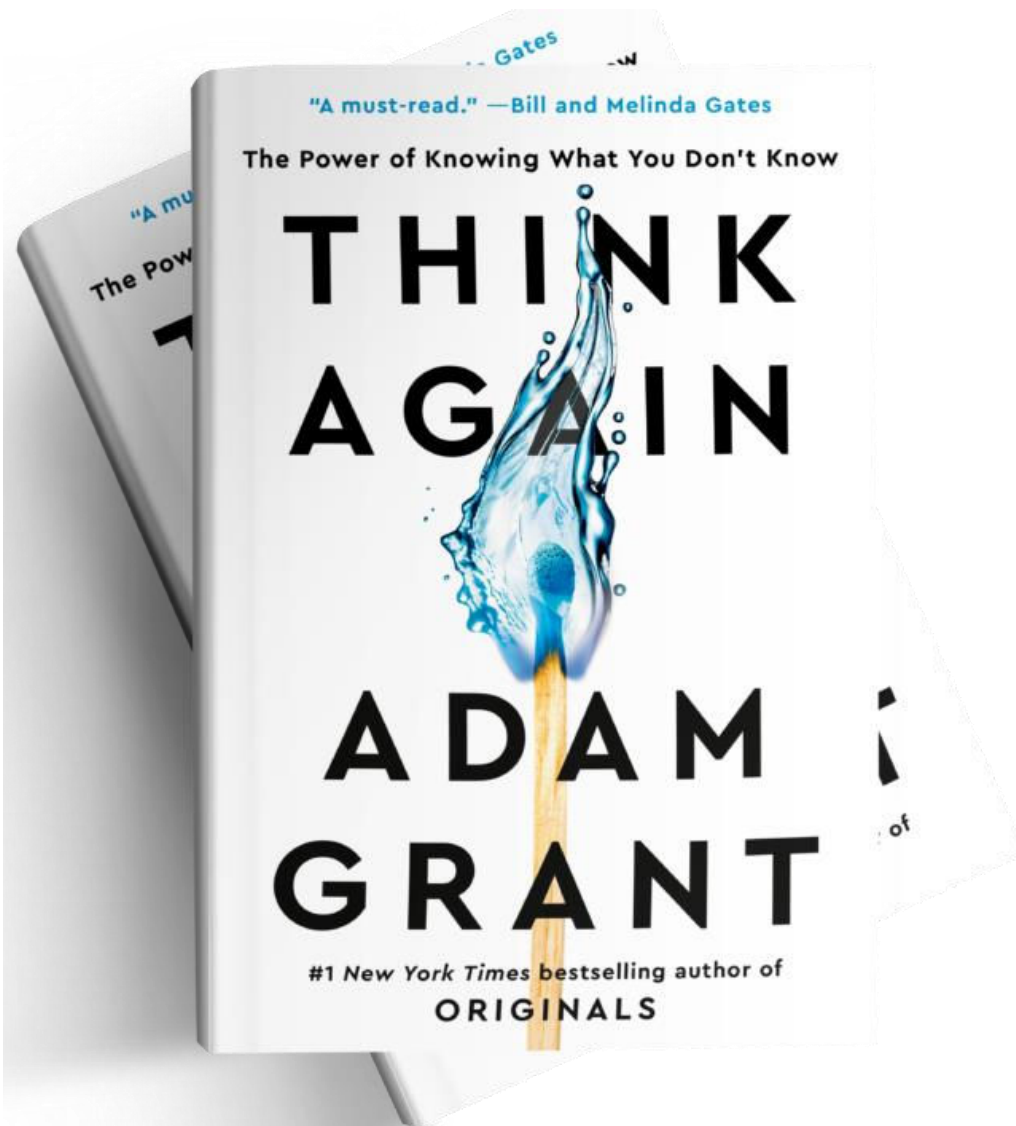
letter

A promoter mutation in the *XIST* gene in two unrelated families with skewed X-chromosome inactivation

Robert M. Plenge¹, Brian D. Hendrich¹, Charles Schwartz², J. Fernando Arena³, Anna Naumova⁴, Carmen Sapienza⁴, Robin M. Winter⁵ & Huntington F. Willard¹

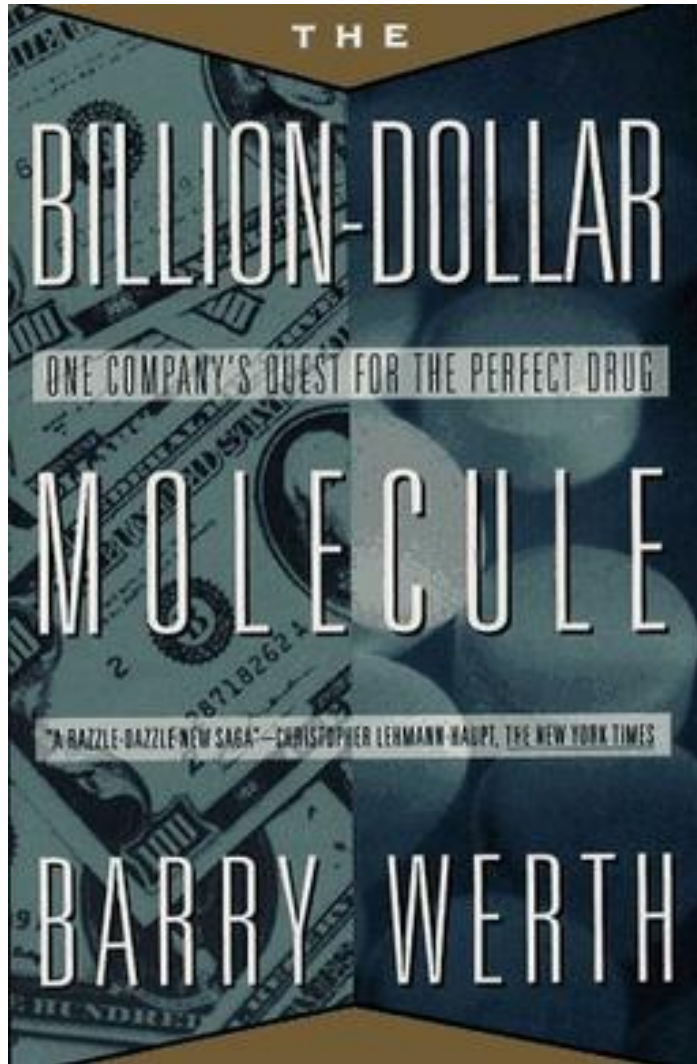


Question YOUR assumptions...challenge YOUR identity



“Part of the problem is **cognitive laziness**. Some psychologists point out that we’re mental misers: we often prefer the ease of hanging on to old views over the difficulty of grappling with new ones. Yet there are also deeper forces behind our resistance to rethinking. **Questioning ourselves makes the world more unpredictable**. It requires us to admit that the facts may have changed, that what was once right may now be wrong. *Reconsidering something we believe deeply can threaten our identities, making it feel as if we’re losing a part of ourselves.*”

Be curious, be courageous, and go deep



Be Curious

"The important thing is to never stop questioning."

— Albert Einstein

Be Courageous

"Nothing in life is to be feared, it is only to be understood."

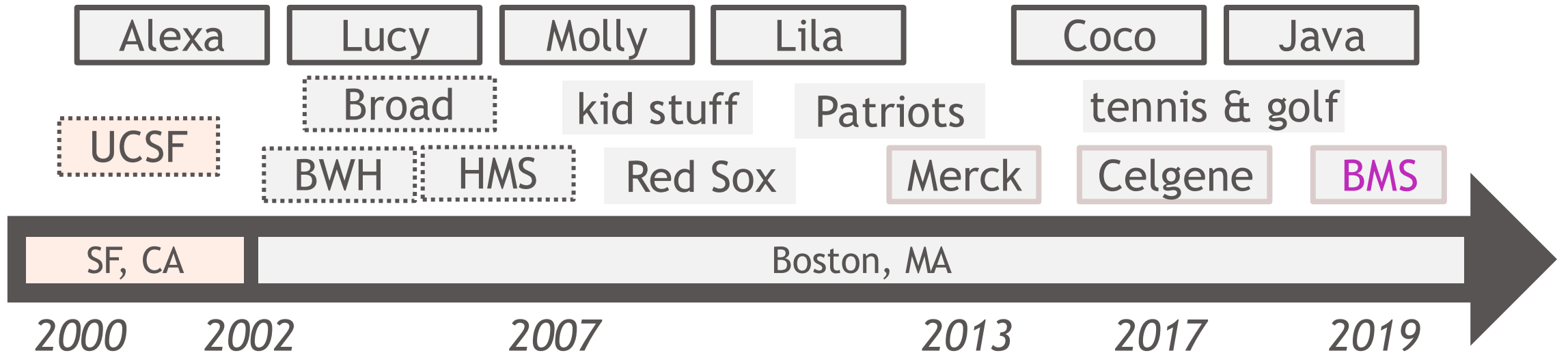
— Marie Curie

Go Deep

"Research is to see what everybody else has seen, and to think what nobody else has thought."

— Albert Szent-Györgyi

My post-graduate years



My post-doc years - *finding alleles, genes, and pathways*

Am. J. Hum. Genet. 77:1044–1060, 2005

Replication of Putative Candidate-Gene Associations with Rheumatoid Arthritis in >4,000 Samples from North America and Sweden: Association of Susceptibility with *PTPN22*, *CTLA4*, and *PADI4*

Robert M. Plenge,^{2,5} Leonid Padyukov,⁹ Elaine F. Remmers,¹¹ Shaun Purcell,⁷ Annette T. Lee,¹² Elizabeth W. Karlson,⁵ Frederick Wolfe,¹³ Daniel L. Kastner,¹¹ Lars Alfredsson,¹⁰ David Altshuler,^{1,3,4,8} Peter K. Gregersen,¹² Lars Klareskog,⁹ and John D. Rioux^{2,6,14}

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

TRAF1–C5 as a Risk Locus for Rheumatoid Arthritis — A Genomewide Study

Robert M. Plenge, M.D., Ph.D., Mark Seielstad, Ph.D., Leonid Padyukov, M.D., Ph.D., Annette T. Lee, Ph.D., Elaine F. Remmers, Ph.D., Bo Ding, Ph.D., Anthony Liew, M.S., Houman Khalili, B.S., Alamelu Chandrasekaran, Ph.D., Leela R.L. Davies, B.S., Wentian Li, Ph.D., Adrian K.S. Tan, M.Sc., Carine Bonnard, M.Sc., Rick T.H. Ong, M.Sc., Anbupalam Thalamuthu, Ph.D., Sven Pettersson, M.D., Ph.D., Chunyu Liu, Ph.D., Chao Tian, B.S., Wei V. Chen, M.S., John P. Carulli, Ph.D., Evan M. Beckman, M.D., David Altshuler, M.D., Ph.D., Lars Alfredsson, Ph.D., Lindsey A. Criswell, M.D., M.P.H., Christopher I. Amos, Ph.D., Michael F. Seldin, M.D., Ph.D., Daniel L. Kastner, M.D., Ph.D., Lars Klareskog, M.D., Ph.D., and Peter K. Gregersen, M.D.*

Two independent alleles at 6q23 associated with risk of rheumatoid arthritis

Robert M Plenge^{1–3}, Chris Cotsapas^{1,3}, Leela Davies¹, Alkes L Price^{1,4}, Paul I W de Bakker^{1,3,4}, Julian Maller^{1,3}, Itsik Pe'er⁵, Noel P Burt¹, Brendan Blumenstiel¹, Matt DeFelice¹, Melissa Parkin¹, Rachel Barry¹, Wendy Winslow¹, Claire Healy¹, Robert R Graham^{1,3}, Benjamin M Neale^{1,3,6}, Elena Izmailova⁷, Ronenn Roubenoff⁷, Alexander N Parker⁷, Roberta Glass², Elizabeth W Karlson², Nancy Maher², David A Hafler^{1,8}, David M Lee², Michael F Seldin⁹, Elaine F Remmers¹⁰, Annette T Lee¹¹, Leonid Padyukov¹², Lars Alfredsson¹³, Jonathan Coby², Michael E Weinblatt², Stacey B Gabriel¹, Shaun Purcell^{1,3}, Lars Klareskog¹², Peter K Gregersen¹¹, Nancy A Shadick², Mark J Daly^{1,3} & David Altshuler^{1,3,4}



My faculty years - *three pillars of exploration*

Genetic discovery	Functional interrogation	Embedded genomics
Common variants at <i>CD40</i> and other loci confer risk of rheumatoid arthritis Soumya Raychaudhuri¹⁻³, Elaine F Remmers⁴, Annette T Lee⁵, Rachel Hackett¹, Candace Guiducci¹, Noël P Burt¹, Lauren Gianniny¹, Benjamin D Korman⁴, Leonid Padyukov⁶, Fina A S Kurreeman⁷, Monica Chang⁸, Joseph J Catanese⁸, Bo Ding⁹, Sandra Wong¹, Annette H M van der Helm-van Mil⁷, Benjamin M Neale^{1-3,10}, Jonathan Cobllyn², Jing Cui², Paul P Tak^{1,1}, Gert Jan Wolbink^{12,13}, J Bart A Crusius¹⁴, Irene E van der Horst-Bruinsma¹⁵, Lindsey A Criswell¹⁶, Christopher I Amos¹⁷, Michael F Seldin¹⁸, Daniel L Kastner⁴, Kristin G Ardlie^{1,19}, Lars Alfredsson⁹, Karen H Costenbader², David Altshuler^{1,3}, Tom W J Huizinga⁷, Nancy A Shadick², Michael E Weinblatt², Nick de Vries¹¹, Jane Worthington²⁰, Mark Seielstad²¹, Rene E M Toes⁷, Elizabeth W Karlson², Ann B Begovich⁸, Lars Klareskog⁶, Peter K Gregersen⁵, Mark J Daly^{1,3} & Robert M Plenge¹⁻³ <i>De novo</i> copy number variants identify new genes and loci in isolated sporadic tetralogy of Fallot Steven C Greenway¹, Alexandre C Pereira², Jennifer C Lin¹, Steven R DePalma¹, Samuel J Israel¹, Sonia M Mesquita², Emel Ergul¹, Jessie H Conta³, Joshua M Korn^{1,4}, Steven A McCarroll^{1,4}, Joshua M Gorham¹, Stacey Gabriel^{1,4}, David M Altshuler^{1,4}, Maria de Lourdes Quintanilla-Dieck^{1,5}, Maria Alexandra Artunduaga^{1,5}, Roland D Eavey³, Robert M Plenge^{4,6}, Nancy A Shadick⁶, Michael E Weinblatt⁶, Philip L De Jager^{4,7}, David A Hafler^{4,7}, Roger E Breitbart³, Jonathan G Seidman^{1,9} & Christine E Seidman^{1,8,9} Bayesian inference analyses of the polygenic architecture of rheumatoid arthritis Eli A Stahl^{11-3*}, Daniel Wegmann⁴, Gosia Trynka⁵, Javier Gutierrez-Achury⁵, Ron Do^{2,6}, Benjamin F Voight⁷, Peter Kraft⁸, Robert Chen¹⁻³, Henrik J Kallberg³, Fina A S Kurreeman¹⁻³, Diabetes Genetics Replication and Meta-analysis Consortium¹⁰, Myocardial Infarction Genetics Consortium¹⁰, Sekar Kathiresan^{2,6}, Cisca Wijmenga⁵, Peter K Gregersen¹¹, Lars Alfredsson⁹, Katherine A Siminovitch¹², Jane Worthington¹³, Paul I W de Bakker^{2,3,14,15}, Soumya Raychaudhuri^{1-3,16} & Robert M Plenge^{1-3,16} LETTER doi:10.1038/nature12873 Genetics of rheumatoid arthritis contributes to biology and drug discovery A list of authors and their affiliations appears at the end of the paper	New variants, genes and pathways in RA Other diseases Highly polygenic architecture Overlap with approved drug targets	

My faculty years - *three pillars of exploration*

Genetic discovery

Common variants at *CD40* and other loci confer risk of rheumatoid arthritis

Soumya Raychaudhuri¹⁻³, Elaine F Remmers⁴, Annette T Lee⁵, Rachel Hackett¹, Candace Guiducci¹, Noël P Burt¹, Lauren Gianniny¹, Benjamin D Korman⁴, Leonid Padyukov⁶, Fina A S Kurreeman⁷, Monica Chang⁸, Joseph J Catanese⁸, Bo Ding⁹, Sandra Wong¹, Annette H M van der Helm-van Mil⁷, Benjamin M Neale^{1-3,10}, Jonathan Cobllyn², Jing Cui², Paul P Tak^{1,1}, Gert Jan Wolbink^{12,13}, J Bart A Crusius¹⁴, Irene E van der Horst-Bruinsma¹⁵, Lindsey A Criswell¹⁶, Christopher I Amos¹⁷, Michael F Seldin¹⁸, Daniel L Kastner⁴, Kristin G Ardlie^{1,19}, Lars Alfredsson⁹, Karen H Costenbader², David Altshuler^{1,3}, Tom W J Huizinga⁷, Nancy A Shadick², Michael E Weinblatt², Nick de Vries¹¹, Jane Worthington²⁰, Mark Seielstad²¹, Rene E M Toes⁷, Elizabeth W Karlson², Ann B Begovich⁸, Lars Klareskog⁶, Peter K Gregersen⁵, Mark J Daly^{1,3} & Robert M Plenge¹⁻³

De novo copy number variants identify new genes and loci in isolated sporadic tetralogy of Fallot

Steven C Greenway¹, Alexandre C Pereira², Jennifer C Lin¹, Steven R DePalma¹, Samuel J Israel¹, Sonia M Mesquita², Emel Ergul¹, Jessie H Conta³, Joshua M Korn^{1,4}, Steven A McCarroll^{1,4}, Joshua M Gorham¹, Stacey Gabriel^{1,4}, David M Altshuler^{1,4}, Maria de Lourdes Quintanilla-Dieck^{1,5}, Maria Alexandra Artunduaga^{1,5}, Roland D Eavey³, Robert M Plenge^{4,6}, Nancy A Shadick⁶, Michael E Weinblatt⁶, Philip L De Jager^{4,7}, David A Hafler^{4,7}, Roger E Breitbart³, Jonathan G Seidman^{1,9} & Christine E Seidman^{1,8,9}

Bayesian inference analyses of the polygenic architecture of rheumatoid arthritis

Eli A Stahl^{1-3*}, Daniel Wegmann⁴, Gosia Trynka⁵, Javier Gutierrez-Achury⁵, Ron Do^{2,6}, Benjamin F Voight⁷, Peter Kraft⁸, Robert Chen¹⁻³, Henrik J Kallberg⁹, Fina A S Kurreeman¹⁻³, Diabetes Genetics Replication and Meta-analysis Consortium¹⁰, Myocardial Infarction Genetics Consortium¹⁰, Sekar Kathiresan^{2,6}, Cisca Wijmenga⁵, Peter K Gregersen¹¹, Lars Alfredsson⁹, Katherine A Siminovitch¹², Jane Worthington¹³, Paul I W de Bakker^{2,3,14,15}, Soumya Raychaudhuri^{1-3,16} & Robert M Plenge^{1-3,16}

LETTER

doi:10.1038/nature12873

Genetics of rheumatoid arthritis contributes to biology and drug discovery

A list of authors and their affiliations appears at the end of the paper

Functional interrogation

OPEN ACCESS Freely available online

PLOS GENETICS

Human Genetics in Rheumatoid Arthritis Guides a High-Throughput Drug Screen of the CD40 Signaling Pathway

Gang Li¹, Dorothée Diogo^{1,2}, Di Wu^{1,2,3}, Jim Spoonamore⁴, Vlado Dancik⁵, Lude Franke⁶, Fina Kurreeman^{1,2}, Elizabeth J. Rossin^{2,7,8}, Grant Duclos¹, Cathy Hartland⁴, Xuezhong Zhou⁹, Kejie Li⁵, Jun Liu³, Philip L. De Jager^{2,10}, Katherine A. Siminovitch^{11,12}, Alexandra Zhernakova^{6,13}, Soumya Raychaudhuri^{1,2}, John Bowes^{14,15}, Steve Eyre^{14,15}, Leonid Padyukov¹⁶, Peter K. Gregersen¹⁷, Jane Worthington^{14,15}, Rheumatoid Arthritis Consortium International (RACI), Namrata Gupta², Paul A. Clemons⁵, Eli Stahl^{1,2}, Nicola Tolliday⁴, Robert M. Plenge^{1,2*}

RESEARCH ARTICLE

Somatic Variation of T-Cell Receptor Genes Strongly Associate with HLA Class Restriction

Paul L. Klarenbeek^{1,2,3,4}, Marieke E. Doorenspleet^{3,4}, Rebecca E. E. Esveldt³, Barbera D. C. van Schaik⁵, Neubury Lardy⁶, Antoine H. C. van Kampen⁵, Paul P. Tak^{3a,b}, Robert M. Plenge^{1,2a,c}, Frank Baas⁴, Paul I. W. de Bakker^{1,2,7,8,w,*}, Niek de Vries^{3w}

PhIP-Seq characterization of autoantibodies from patients with multiple sclerosis, type 1 diabetes and rheumatoid arthritis

H. Benjamin Larman^{a,b,c,d,*,*}, Uri Laserson^{a,e,f}, Luis Querol^{g,h,n}, Katrijn Verhaeghenⁱ, Nicole L. Solimini^{c,d}, George Jing Xu^{a,c,d,p}, Paul L. Klarenbeek¹, George M. Church^f, David A. Hafler^{g,h}, Robert M. Plenge^{j,q}, Peter A. Nigrovic^{j,k}, Philip L. De Jager¹, Ilse Weets^{l,m}, Geert A. Martensⁱ, Kevin C. O'Connor^o, Stephen J. Elledge^{c,d,*}

OPEN ACCESS Freely available online

PLOS ONE

Allele-Specific Methylation Occurs at Genetic Variants Associated with Complex Disease

John N. Hutchinson^{1,2*}, Towfique Raj^{3,4}, Jes Fagerness⁵, Eli Stahl¹, Fernando T. Viloria³, Alexander Gimelbrant^{6,7}, Johanna Seddon^{8,9}, Mark Daly⁵, Andrew Chess¹⁰, Robert Plenge¹

Embedded genomics

Assays for phenotypic drug screens

Connect variants and genes with biological pathways and mechanisms

Genetic discovery	Functional interrogation	Embedded genomics
Common variants at <i>CD40</i> and other loci confer risk of rheumatoid arthritis Soumya Raychaudhuri^{1–3}, Elaine F Remmers⁴, Annette T Lee⁵, Rachel Hackett¹, Candace Guiducci¹, Noël P Burt¹, Lauren Gianniny¹, Benjamin D Korman⁴, Leonid Padyukov⁶, Fina A S Kurreeman⁷, Monica Chang⁸, Joseph J Catanese⁸, Bo Ding⁹, Sandra Wong¹, Annette H M van der Helm-van Mil⁷, Benjamin M Neale^{1,3,10}, Jonathan Coby², Jing Cui², Paul P Tak¹¹, Gert Jan Wolbink^{12,13}, J Bart A Crusius¹⁴, Irene E van der Horst-Bruinsma¹⁵, Lindsey A Criswell¹⁶, Christopher I Amos¹⁷, Michael F Seldin¹⁸, Daniel L Kastner⁴, Kristin G Ardlie^{1,19}, Lars Alfredsson⁹, Karen H Costenbader², David Altshuler^{1,3}, Tom W J Huizinga⁷, Nancy A Shadick², Michael E Weinblatt², Niek de Vries¹¹, Jane Worthington²⁰, Mark Seielstad²¹, Rene E M Toes⁷, Elizabeth W Karlson², Ann B Begovich⁸, Lars Klareskog⁶, Peter K Gregersen⁵, Mark J Daly^{1,3} & Robert M Plenge^{1–3} <i>De novo</i> copy number variants identify new genes and loci in isolated sporadic tetralogy of Fallot Steven C Greenawald¹, Alexandre C Pereira², Jennifer C Lin¹, Steven R DePalma¹, Samuel J Israel¹, Sonia M Mesquita², Emel Ergul³, Jessie H Conta³, Joshua M Korn^{1,4}, Steven A McCarroll^{1,4}, Joshua M Gorham¹, Stacey Gabriel⁴, David M Altshuler^{1,4}, Maria de Lourdes Quintanilla-Dieck^{1,5}, Maria Alexandra Artunduaga^{1,5}, Roland D Eavey⁶, Robert M Plenge^{4,6}, Nancy A Shadick⁶, Michael E Weinblatt⁶, Philip L De Jager^{4,7}, David A Hafler^{4,7}, Roger E Breitbart⁸, Jonathan G Seidman^{1,9} & Christine E Seidman^{1,8,9} Bayesian inference analyses of the polygenic architecture of rheumatoid arthritis Eli A Stahl^{1–3*}, Daniel Wegmann⁴, Gosia Trynka⁵, Javier Gutierrez-Achury⁵, Ron Do^{2,6}, Benjamin F Voight⁷, Peter Kraft⁸, Robert Chen^{1–3}, Henrik J Kallberg⁹, Fina A S Kurreeman^{1–3}, Diabetes Genetics Replication and Meta-analysis Consortium¹⁰, Myocardial Infarction Genetics Consortium¹⁰, Sekar Kathiresan^{2,6}, Cisca Wijmenga⁵, Peter K Gregersen¹¹, Lars Alfredsson⁹, Katherine A Siminovitch¹², Jane Worthington¹³, Paul I W de Bakker^{2,3,14,15}, Soumya Raychaudhuri^{1–3,16} & Robert M Plenge^{1–3,16}	Human Genetics in Rheumatoid Arthritis Guides a High-Throughput Drug Screen of the CD40 Signaling Pathway Gang Li¹, Dorothée Diogo^{1,2}, Di Wu^{1,2,3}, Jim Spoonamore⁴, Vlado Dancik⁵, Lude Franke⁶, Fina Kurreeman^{1,2}, Elizabeth J. Rossin^{2,7,8}, Grant Duclos¹, Cathy Hartland⁴, Xuezhong Zhou⁹, Kejie Li⁵, Jun Liu³, Philip L. De Jager^{2,10}, Katherine A. Siminovitch^{11,12}, Alexandra Zhernakova^{6,13}, Soumya Raychaudhuri^{1,2}, John Bowes^{14,15}, Steve Eyre^{14,15}, Leonid Padyukov¹⁶, Peter K. Gregersen¹⁷, Jane Worthington^{14,15}, Rheumatoid Arthritis Consortium International (RACI), Namrata Gupta², Paul A. Clemons⁵, Eli Stahl^{1,2}, Nicola Tolliday⁴, Robert M. Plenge^{1,2*} RESEARCH ARTICLE Somatic Variation of T-Cell Receptor Genes Strongly Associate with HLA Class Restriction Paul L. Klarenbeek^{1,2,3,4}, Marieke E. Doorenspleet^{3,4}, Rebecca E. E. Esvelde³, Barbera D. C. van Schaik⁵, Neubury Lardy⁶, Antoine H. C. van Kampen⁵, Paul P. Tak^{3a,b}, Robert M. Plenge^{1,2a,c}, Frank Baas⁴, Paul I. W. de Bakker^{1,2,7,8a,*,}, Niek de Vries^{3a} PhIP-Seq characterization of autoantibodies from patients with multiple sclerosis, type 1 diabetes and rheumatoid arthritis H. Benjamin Larman^{a,b,c,d,*,*}, Uri Laserson^{a,e,f}, Luis Quera^{g,h,n}, Katrijn Verhaeghenⁱ, Nicole L. Solimini^{c,d}, George Jing Xu^{a,c,d,p}, Paul L. Klarenbeek^j, George M. Churchⁱ, David A. Hafler^{g,h}, Robert M. Plenge^{j,q}, Peter A. Nigrovic^{j,k}, Philip L. De Jagerⁱ, Ilse Weets^{l,m}, Geert A. Martensⁱ, Kevin C. O'Connor^o, Stephen J. Elledge^{c,d,*}	Genome-Wide Association Study and Gene Expression Analysis Identifies <i>CD84</i> as a Predictor of Response to Etanercept Therapy in Rheumatoid Arthritis Jing Cui^{1,3}, Eli A. Stahl^{1,2,3,a,b}, Saedis Saevarsdottir^{4,5}, Corinne Miceli^{6,7}, Dorothée Diogo^{1,2,3}, Gosia Trynka^{1,2,3}, Towfique Raj^{2,3,8}, Maša Umičević Mirkov⁹, Helena Canha^{1,10,11}, Katsunori Ikari¹², Chikashi Terao^{13,14}, Yukinori Okada^{1,2,3}, Sara Wedrén^{4,5}, Johan Askling^{4,15}, Hisashi Yamanaka¹², Chikashi Mochizuki¹², Anne Teasdale¹², Keisuke Ohnawa¹², Eumilike Matsuda¹⁴, Tetsuya Mima¹³ Germline PGx is complex... Kene E. M. Toes^{a,*}, Robert P. Kimberly^{b,*}, S. Louis Bridges Jr.^{c,*}, Lindsey A. Criswell^{d,*}, Larry W. Moreland^{e,*}, João Eurico Fonseca^{10,11}, Niek de Vries²⁰, Barbara E. Stranger^{2,3}, Philip L. De Jager^{2,3,7}, Soumya Raychaudhuri^{1,2,3,32}, Michael E. Weinblatt¹, Peter K. Gregersen³³, Xavier Mariette^{6,7}, Anne Barton³⁴, Leonid Padyukov², Marieke J. H. Coenen², Elizabeth W. Karlson¹, Robert M. Plenge^{1,2,3*} RESEARCH ARTICLE TYK2 Protein-Coding Variants Protect against Rheumatoid Arthritis and Autoimmunity, with No Evidence of Major Pleiotropic Effects on Non-Autoimmune Complex Traits Dorothée Diogo^{1,2,3,4,a,b}, Lisa Bastarache⁵, Katherine P. Liao¹, Robert R. Graham⁶, Robert S. Fulton⁷, Jeffrey D. Greenberg⁸, Steve Eyre⁹, John Bowes⁹, Jing Cui¹, Annette Lee¹⁰, Benjamin F. Voight¹¹, Peter Kraft¹², Henrik J. Kallberg¹³, Fina A. S. Kurreeman¹⁴, Cisca Wijmenga¹⁵, Peter K. Gregersen¹⁶, Lars Alfredsson¹⁷, Jane Worthington¹⁸, Paul I. W. de Bakker¹⁹, Soumya Raychaudhuri^{1–3,16} & Robert M. Plenge^{1–3,16}
LETTER Genetics of rheumatoid arthritis contributes to biology and drug discovery A list of authors and their affiliations appears at the end of the paper	Allele-Specific Methylation Occurs at Genetic Variants Associated with Complex Disease John N. Hutchinson^{1,2*}, Towfique Raj^{3,4}, Jes Fagerness⁵, Eli Stahl¹, Fernando T. Viloria³, Alexander Gimelbrant^{6,7}, Johanna Seddon^{8,9}, Mark Daly⁵, Andrew Chess¹⁰, Robert Plenge¹	...but germline genetics points to new drug targets. Jane Worthington⁹, Elaine R. Mardis⁷, Michael F. Seldin²⁴, Peter K. Gregersen¹⁰, Timothy Behrens⁵, Soumya Raychaudhuri^{1,2,3,4,9}, Joshua C. Denny^{5,30}, Robert M. Plenge^{1,2,3,a,b}

My faculty years - research converged on **drug discovery**

Genetic discovery

Common variants at *CD40* and other loci confer risk of rheumatoid arthritis

Soumya Raychaudhuri¹⁻³, Elaine F Remmers⁴, Annette T Lee⁵, Rachel Hackett¹, Candace Guiducci¹, Noël P Burt¹, Lauren Giannini¹, Benjamin D Korman⁴, Leonid Padyukov⁶, Fina A S Kurreeman⁷, Monica Chang⁸, Joseph J Catanese⁸, Bo Ding⁹, Sandra Wong¹, Annette H M van der Helm-van Mil⁷, Benjamin M Neale^{1,3,10}, Jonathan Cobllyn², Jing Cui², Paul P Tak^{1,1}, Gert Jan Wolbink^{12,13}, J Bart A Crusius¹⁴, Irene E van der Horst-Bruinsma¹⁵, Lindsey A Criswell¹⁶, Christopher I Amos¹⁷, Michael F Seldin¹⁸, Daniel L Kastner⁴, Kristin G Ardlie^{1,19}, Lars Alfredsson⁹, Karen H Costenbader², David Altshuler^{1,3}, Tom W J Huizinga⁷, Nancy A Shadick², Michael E Weinblatt², Nick de Vries¹¹, Jane Worthington²⁰, Mark Seielstad²¹, Rene E M Toes⁷, Elizabeth W Karlson², Ann B Begovich⁸, Lars Klareskog⁶, Peter K Gregersen⁵, Mark J Daly^{1,3} & Robert M Plenge¹⁻³

De novo copy number variants identify new genes and loci in isolated sporadic tetralogy of Fallot

Steven C Greenway¹, Alexandre C Pereira², Jennifer C Lin¹, Steven R DePalma¹, Samuel J Israel¹, Sonia M Mesquita², Emel Ergul¹, Jessie H Conta³, Joshua M Korn^{1,4}, Steven A McCarroll^{1,4}, Joshua M Gorham¹, Stacey Gabriel^{1,4}, David M Altshuler^{1,4}, Maria de Lourdes Quintanilla-Dieck^{1,5}, Maria Alexandra Artunduaga^{1,5}, Roland D Eavey², Robert M Plenge^{6,6}, Nancy A Shadick⁶, Michael E Weinblatt⁶, Philip L De Jager^{4,7}, David A Hafler^{4,7}, Roger E Breitbart³, Jonathan G Seidman^{1,9} & Christine E Seidman^{1,8,9}

Bayesian inference analyses of the polygenic architecture of rheumatoid arthritis

Eli A Stahl^{1-3*}, Daniel Wegmann⁴, Gosia Trynka⁵, Javier Gutierrez-Achury⁵, Ron Do^{2,6}, Benjamin F Voight⁷, Peter Kraft⁸, Robert Chen¹⁻³, Henrik J Kallberg⁹, Fina A S Kurreeman¹⁻³, Diabetes Genetics Replication and Meta-analysis Consortium¹⁰, Myocardial Infarction Genetics Consortium¹⁰, Sekar Kathiresan^{2,6}, Cisca Wijmenga⁵, Peter K Gregersen¹¹, Lars Alfredsson⁹, Katherine A Siminovich¹², Jane Worthington¹³, Paul I W de Bakker^{2,3,14,15}, Soumya Raychaudhuri^{1-3,16} & Robert M Plenge^{1-3,16}

LETTER

doi:10.1038/nature12873

Genetics of rheumatoid arthritis contributes to biology and drug discovery

A list of authors and their affiliations appears at the end of the paper

Functional interrogation

OPEN ACCESS Freely available online

PLOS GENETICS

Human Genetics in Rheumatoid Arthritis Guides a High-Throughput Drug Screen of the CD40 Signaling Pathway

Gang Li¹, Dorothée Diogo^{1,2}, Di Wu^{1,2,3}, Jim Spoonamore⁴, Vlado Dancik⁵, Lude Franke⁶, Fina Kurreeman^{1,2}, Elizabeth J. Rossin^{2,7,8}, Grant Duclos⁷, Cathy Hartland⁴, Xuezhong Zhou⁹, Kejie Li⁵, Jun Liu³, Philip L. De Jager^{2,10}, Katherine A. Siminovich^{11,12}, Alexandra Zernakova^{6,13}, Soumya Raychaudhuri^{1,2}, John Bowes^{14,15}, Steve Eyre^{14,15}, Leonid Padyukov¹⁶, Peter K. Gregersen¹⁷, Jane Worthington^{14,15}, Rheumatoid Arthritis Consortium International (RACI), Namrata Gupta², Paul A. Clemons⁵, Eli Stahl^{1,2}, Nicola Tolliday⁴, Robert M. Plenge^{1,2*}

RESEARCH ARTICLE

Somatic Variation of T-Cell Receptor Genes Strongly Associate with HLA Class Restriction

Paul L. Klarenbeek^{1,2,3,4}, Marieke E. Doorenspleet^{3,4}, Rebecca E. E. Esveldt³, Barbera D. C. van Schaik⁵, Neubury Lardy⁶, Antoine H. C. van Kampen⁵, Paul P. Tak^{3,6,7,8}, Robert M. Plenge^{1,2,9}, Frank Baas⁴, Paul I. W. de Bakker^{1,2,7,8,9}, Niek de Vries^{3,9}

PhIP-Seq characterization of autoantibodies from patients with multiple sclerosis, type 1 diabetes and rheumatoid arthritis

H. Benjamin Larman^{a,b,c,d,*,*}, Uri Laserson^{a,e,f}, Luis Querol^{g,h,i}, Katrijn Verhaeghenⁱ, Nicole L. Solimini^{c,d}, George Jing Xu^{a,c,d,p}, Paul L. Klarenbeek¹, George M. Churchⁱ, David A. Hafler^{g,h}, Robert M. Plenge^{j,q}, Peter A. Nigrovic^{j,k}, Philip L. De Jager¹, Ilse Weets^{l,m}, Geert A. Martensⁱ, Kevin C. O'Connor^o, Stephen J. Elledge^{c,d,*}

OPEN ACCESS Freely available online

PLOS ONE

Allele-Specific Methylation Occurs at Genetic Variants Associated with Complex Disease

John N. Hutchinson^{1,2*}, Towfique Raj^{3,4}, Jes Fagerness⁵, Eli Stahl¹, Fernando T. Viloria³, Alexander Gimelbrant^{6,7}, Johanna Seddon^{8,9}, Mark Daly⁵, Andrew Chess¹⁰, Robert Plenge¹

Embedded genomics

OPEN ACCESS Freely available online

PLOS GENETICS

Genome-Wide Association Study and Gene Expression Analysis Identifies *CD84* as a Predictor of Response to Etanercept Therapy in Rheumatoid Arthritis

Jing Cui^{1,3}, Eli A. Stahl^{1,2,3,9,10}, Saedis Saevardottir^{4,5}, Corinne Miceli^{6,7}, Dorothée Diogo^{1,2,3}, Gosia Trynka^{1,2,3}, Towfique Raj^{2,3,8}, Maša Umičević Mirkov⁹, Helena Canhao^{1,10,11}, Katsunori Ikari¹², Chikashi Terao^{13,14}, Yukinori Okada^{1,2,3}, Sara Wedrén^{4,5}, Johan Askling^{4,15}, Hisashi Yamanaka¹², Shigeki Momohara¹², Atsuo Taniguchi¹², Koichiro Ohmura¹³, Fumihiko Matsuda¹⁴, Tsuneyo Mimori¹³, Namrata Gupta³, Manik Kuchroo^{3,8}, Ann W. Morgan¹⁶, John D. Isaacs¹⁷, Anthony G. Wilson¹⁸, Kimme L. Hyrich¹⁹, Marieke Herenius²⁰, Marieke E. Doorenspleet²⁰, Paul-Peter Tak^{20,21}, J. Bart A. Crusius²¹, Irene E. van der Horst-Bruinsma²², Gert Jan Wolbink^{23,24,25}, Piet L. C. M. van Riel⁹, Mart van de Laar²⁶, Henk-Jan Guchelaar²⁷, Nancy A. Shadick¹, Cornelia F. Allaart²⁸, Tom W. J. Huizinga²⁸, Rene E. M. Toes²⁸, Robert P. Kimberly²⁹, S. Louis Bridges Jr.²⁹, Lindsey A. Criswell³⁰, Larry W. Moreland³¹, João Eurico Fonseca^{10,11}, Niek de Vries²⁰, Barbara E. Stranger^{2,3}, Philip L. De Jager^{2,3,7}, Soumya Raychaudhuri^{1,2,3,32}, Michael E. Weinblatt¹, Peter K. Gregersen³³, Xavier Mariette^{6,7}, Anne Barton³⁴, Leonid Padyukov⁵, Marieke J. H. Coenen⁹, Elizabeth W. Karlson¹, Robert M. Plenge^{1,2,3*}

RESEARCH ARTICLE

TYK2 Protein-Coding Variants Protect against Rheumatoid Arthritis and Autoimmunity, with No Evidence of Major Pleiotropic Effects on Non-Autoimmune Complex Traits

Dorothée Diogo^{1,2,3,4,5,6,7}, Lisa Bastarache⁵, Katherine P. Liao¹, Robert R. Graham⁶, Robert S. Fulton⁷, Jeffrey D. Greenberg⁸, Steve Eyre⁹, John Bowes⁹, Jing Cui¹, Annette Lee¹⁰

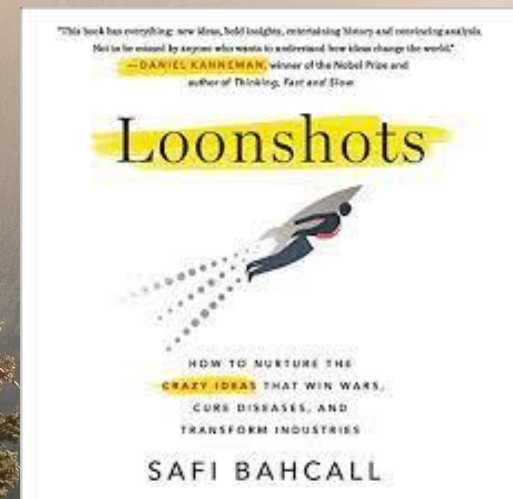
...but germline genetics points to new drug targets.

Jane Worthington⁹, Elaine R. Mardis⁷, Michael F. Seldin²⁴, Peter K. Gregersen¹⁰, Timothy Behrens⁵, Soumya Raychaudhuri^{1,2,3,4,9}, Joshua C. Denny^{5,30}, Robert M. Plenge^{1,2,3,33}

Ask questions...big questions

Work only on problems that are manifestly important and seem to be nearly impossible to solve. That way you will have a natural market for your product and no competition.

Edwin Land

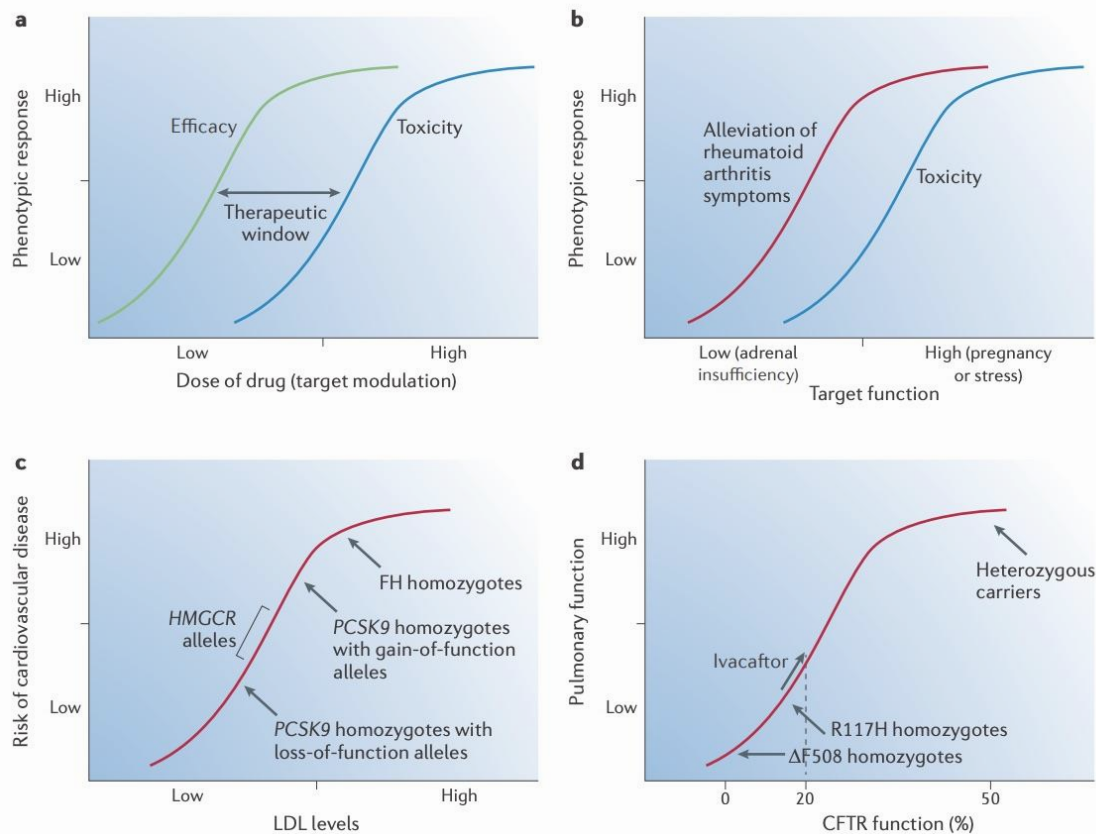


Move to industry - *human genetics to accelerate R&D*

 A GUIDE TO DRUG DISCOVERY

Validating therapeutic targets through human genetics

Robert M. Plenge^{1,2}, Edward M. Scolnick^{2,3} and David Altshuler^{2,4,5}

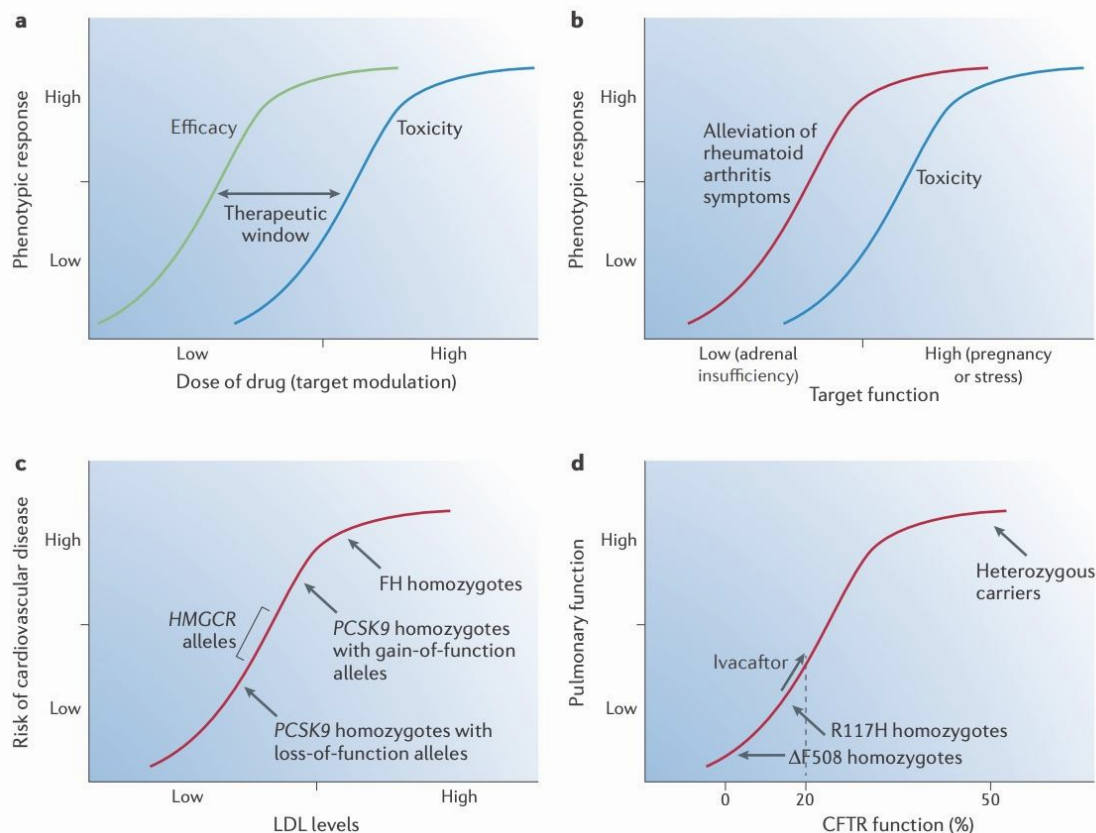


Move to industry - *human genetics to accelerate R&D*

A GUIDE TO DRUG DISCOVERY

Validating therapeutic targets through human genetics

Robert M. Plenge^{1,2}, Edward M. Scolnick^{2,3} and David Altshuler^{2,4,5}



The Man in the Arena

It is not the critic who counts; not the man who points out how the strong man stumbles, or where the doer of deeds could have done them better. **The credit belongs**

to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs, who comes short again and again, because there is no effort without error and shortcoming;

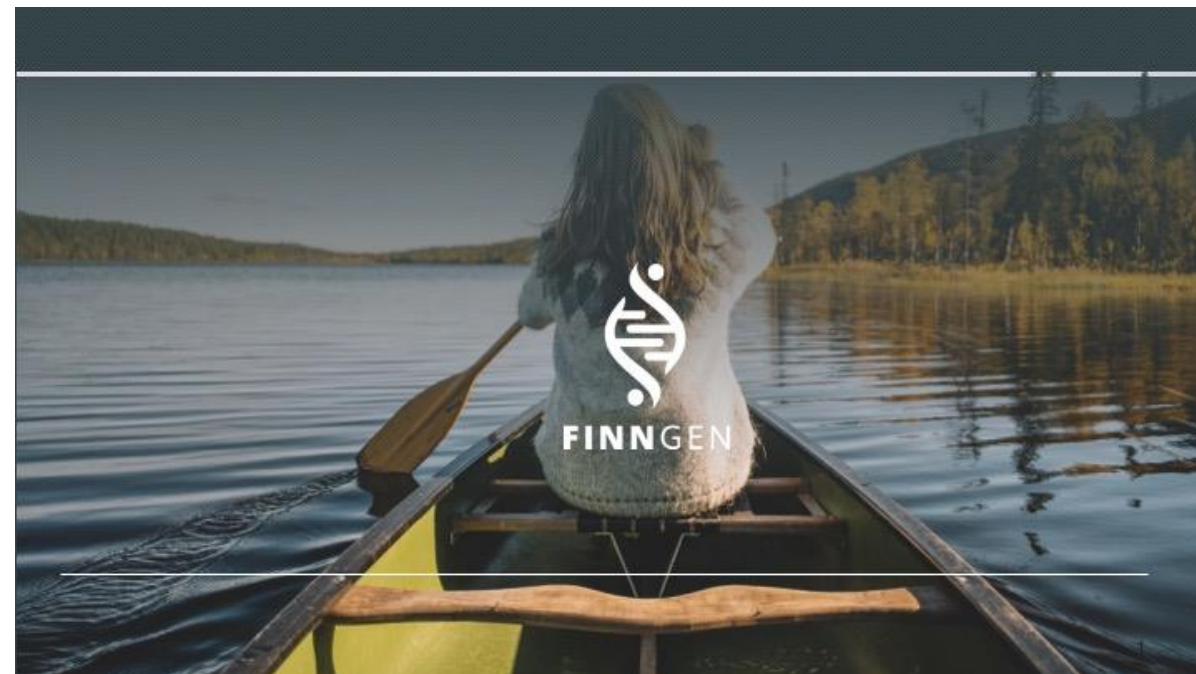
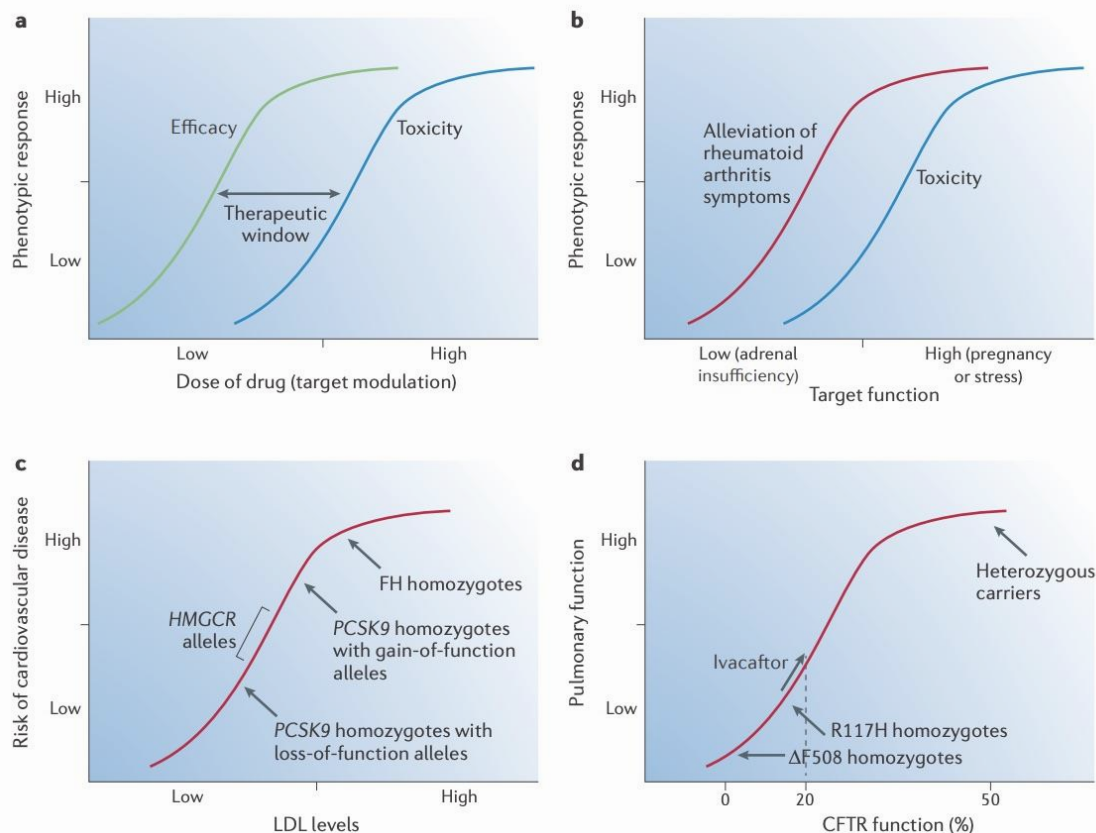
but who does actually strive to do the deeds; who knows great enthusiasms, the great devotions; who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement, and who at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who neither know victory nor defeat.

Move to industry - *human genetics to accelerate R&D*

 A GUIDE TO DRUG DISCOVERY

Validating therapeutic targets through human genetics

Robert M. Plenge^{1,2}, Edward M. Scolnick^{2,3} and David Altshuler^{2,4,5}



Article | Published: 06 June 2018

Genomic atlas of the human plasma proteome

Benjamin B. Sun, Joseph C. Maranville, James E. Peters, David Stacey, James R. Staley, James Blackshaw, Stephen Burgess, Tao Jiang, Ellie Paige, Praveen Surendran, Clare Oliver-Williams, Mihir A. Kamat, Bram P. Prins, Sheri K. Wilcox, Erik S. Zimmerman, An Chi, Narinder Bansal, Sarah L. Spain, Angela M. Wood, Nicholas W. Morrell, John R. Bradley, Nebojsa Janjic, David J. Roberts, Willem H. Ouwehand, John A. Todd, Nicole Soranzo, Karsten Suhre, Dirk S. Paul, Caroline S. Fox, Robert M. Plenge, John Danesh , Heiko Runz & Adam S. Butterworth  - [Show fewer authors](#)

Nature **558**, 73–79(2018) | [Cite this article](#)

Education in industry - *much more than just “new targets”*

Disciplined approach to drug discovery and early development

Robert M. Plenge

Our modern health care system demands therapeutic interventions that improve the lives of patients. Unfortunately, decreased productivity in therapeutics research and development (R&D) has driven drug costs up while delivering insufficient value to patients. Here, I discuss a model of translational medicine that connects four components of the early R&D pipeline—causal human biology, therapeutic modality, biomarkers of target modulation, and proof-of-concept clinical trials. Whereas the individual components of this model are not new, technological advances and a disciplined approach to integrating all four areas offer hope for improving R&D productivity.

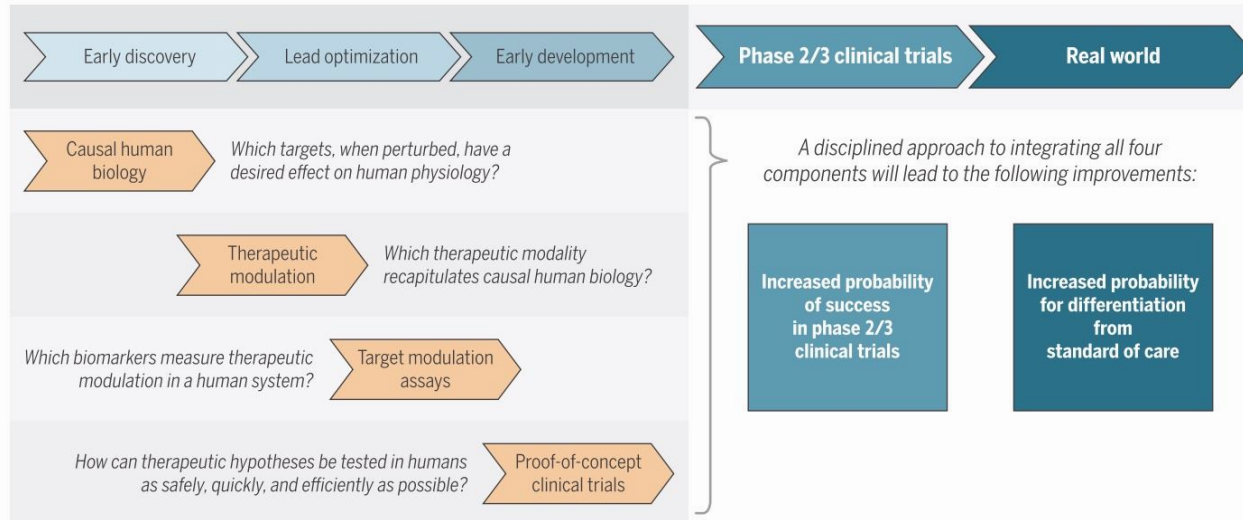


Fig. 1. A disciplined approach to identify drug targets and test therapeutic hypotheses. Four areas in translational medicine are causal human biology, therapeutic modalities that recapitulate human biology, biomarkers of target modulation, and next-generation clinical trial technologies. Connecting all four promises to improve the novelty, efficiency, and productivity of drug R&D.

Refining causal human biology to nominate therapeutic hypotheses

Matching modality to mechanism to invent new medicines

Connecting therapeutic hypothesis with robust translational biomarkers for path to proof-of-concept trials

Iterating on this theme with clinical data to guide development programs and inform on future programs

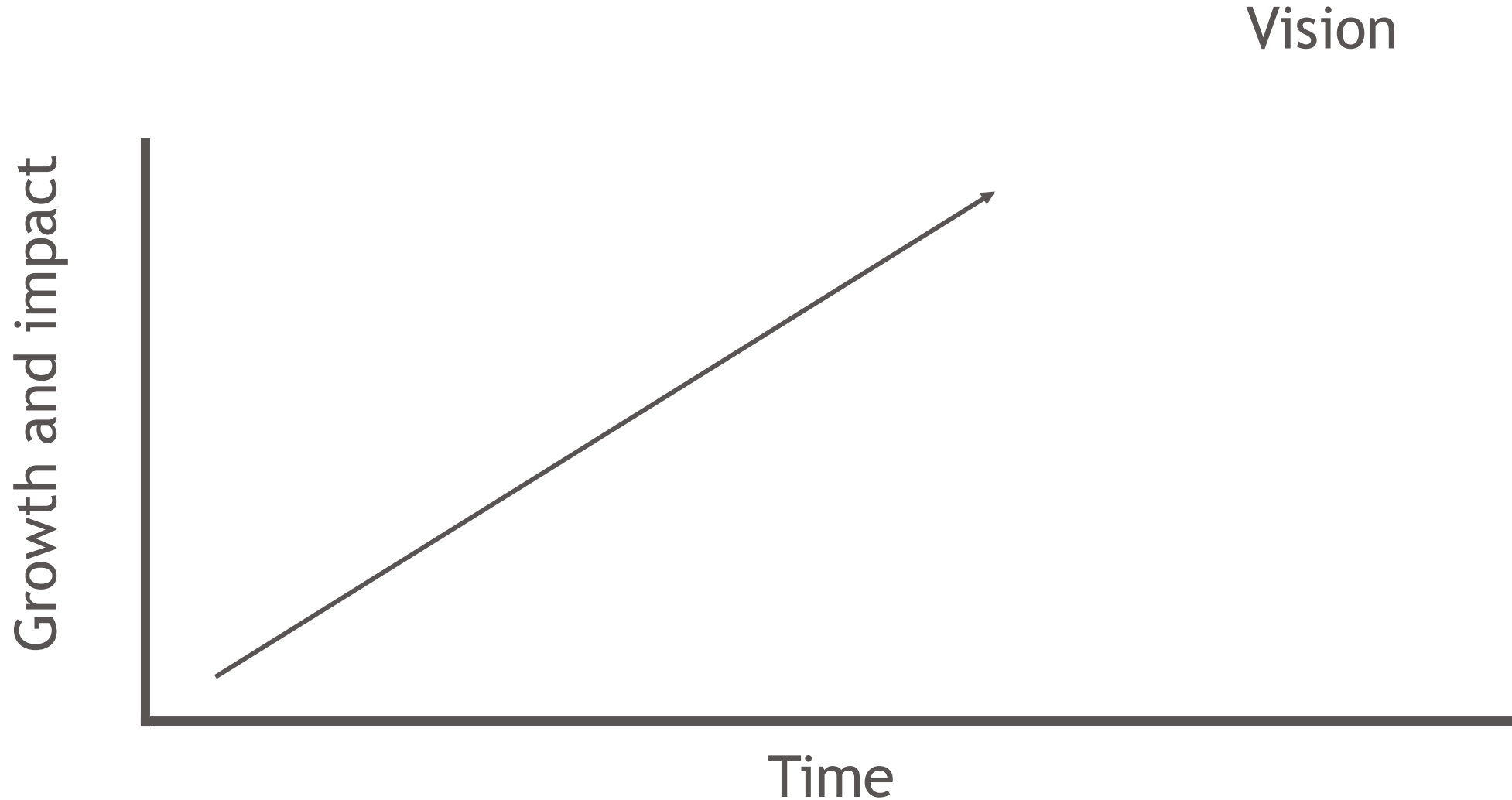
Industry experience: *Merck, Celgene, BMS, Boards*

- **Merck (2013-2017)**
 - Genetics & Pharmacogenomics (GpGx)
 - Translational Medicine (TM)
 - **Celgene (2017-2019)**
 - Immunology & Inflammation (I&I)
 - Alewife (Cambridge) site head
 - **Bristol Myers Squibb (2019-2023)**
 - Immunology, Cardiology, and Fibrosis (ICF) Thematic Research Center (TRC)
 - Translational Medicine (TM)
 - **Board of Directors**
 - Translate Bio (2019-2021)
 - Alltrna (2022-present)
- Broad exposure to R&D across multiple therapeutic areas
- Drive R&ED strategy with the urgency of a smaller company
- Drive R&ED strategy on a larger scale
- Participate in the broader biotech-venture community

Industry experience: *Merck, Celgene, BMS, Boards*

- **Merck (2013-2017)**
 - Genetics & Pharmacogenomics (GpGx)
 - Translational Medicine (TM)
 - **Celgene (2017-2019)**
 - Immunology & Inflammation (I&I)
 - Alewife (Cambridge) site
 - **Bristol Myers Squibb (2019-2022)**
 - Immunology & Inflammation (I&I), Hematology, and Fibrosis Research Center (TRC)
 - Translational Medicine (TM)
 - **Board of Directors**
 - Translate Bio (2019-2021)
 - Alltrna (2022-present)
- Beware of the personal narrative!**
- Broad exposure to multiple areas of the biotech industry
- Drive R&ED strategy with the urgency of a smaller company
- Drive R&ED strategy on a larger scale
- Participate in the broader biotech-venture community

Many think of career development as a straight line



Career development is the natural tension between passion and discipline. With only passion...

Vision

Passion



Discipline

Career development is the natural tension between passion and discipline. With only passion...*unfulfilled dreams*

Vision

Passion

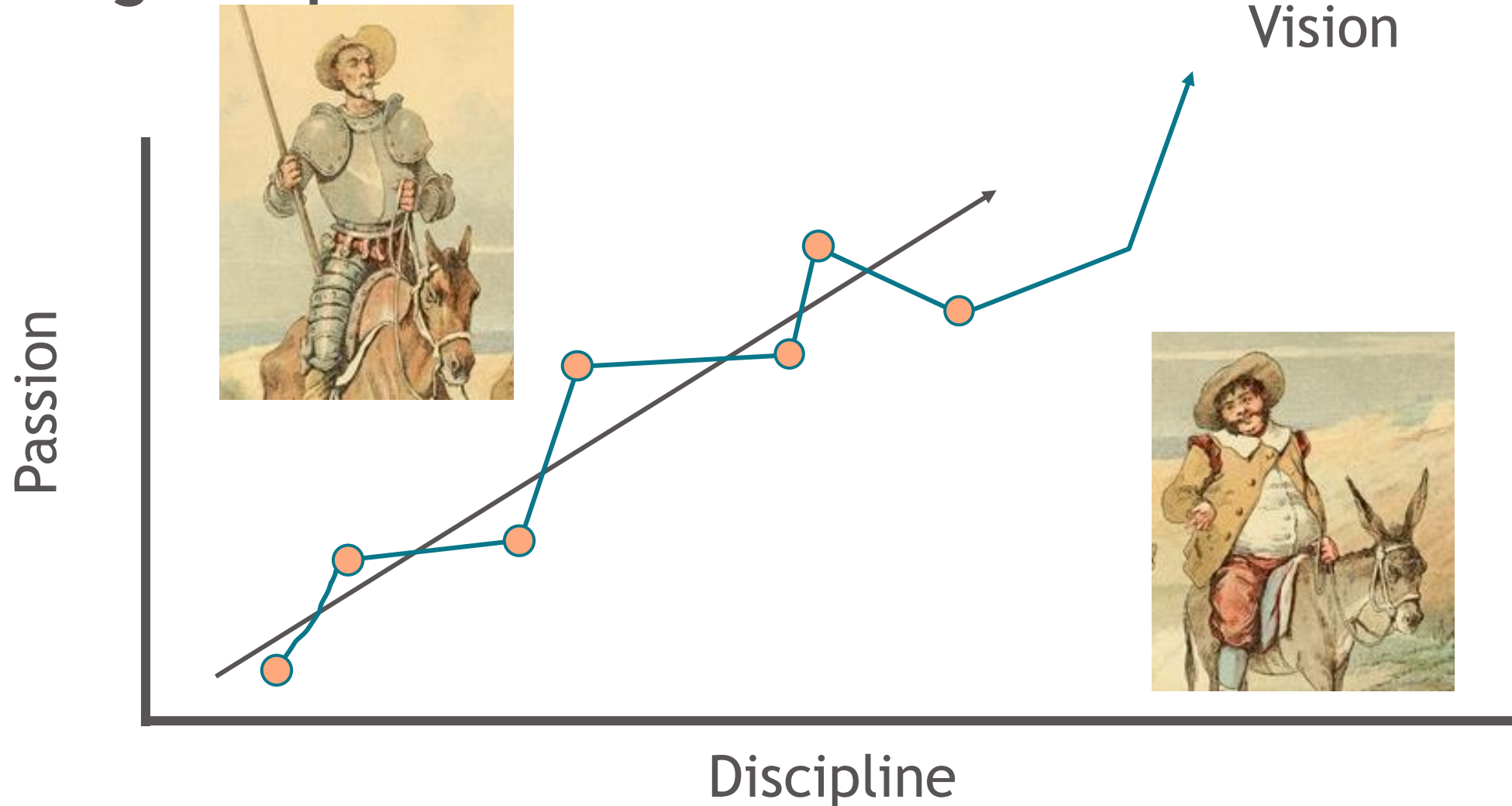


“Quixote does not accept reality, he imposes his *imagination*, his *commitment*, and his *joy* on it. He produces a world of beauty and of meaning.”

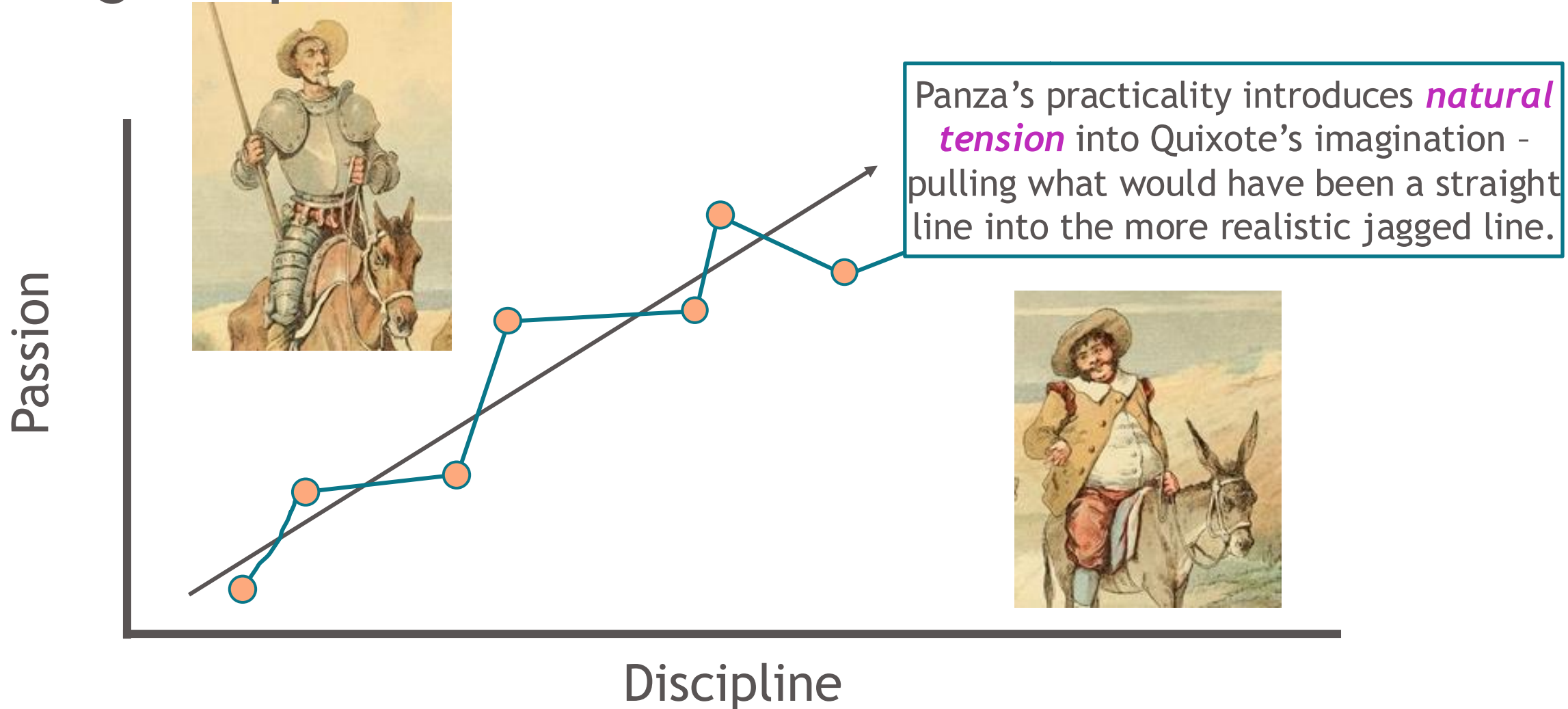
- James March (Stanford Business School)

Discipline

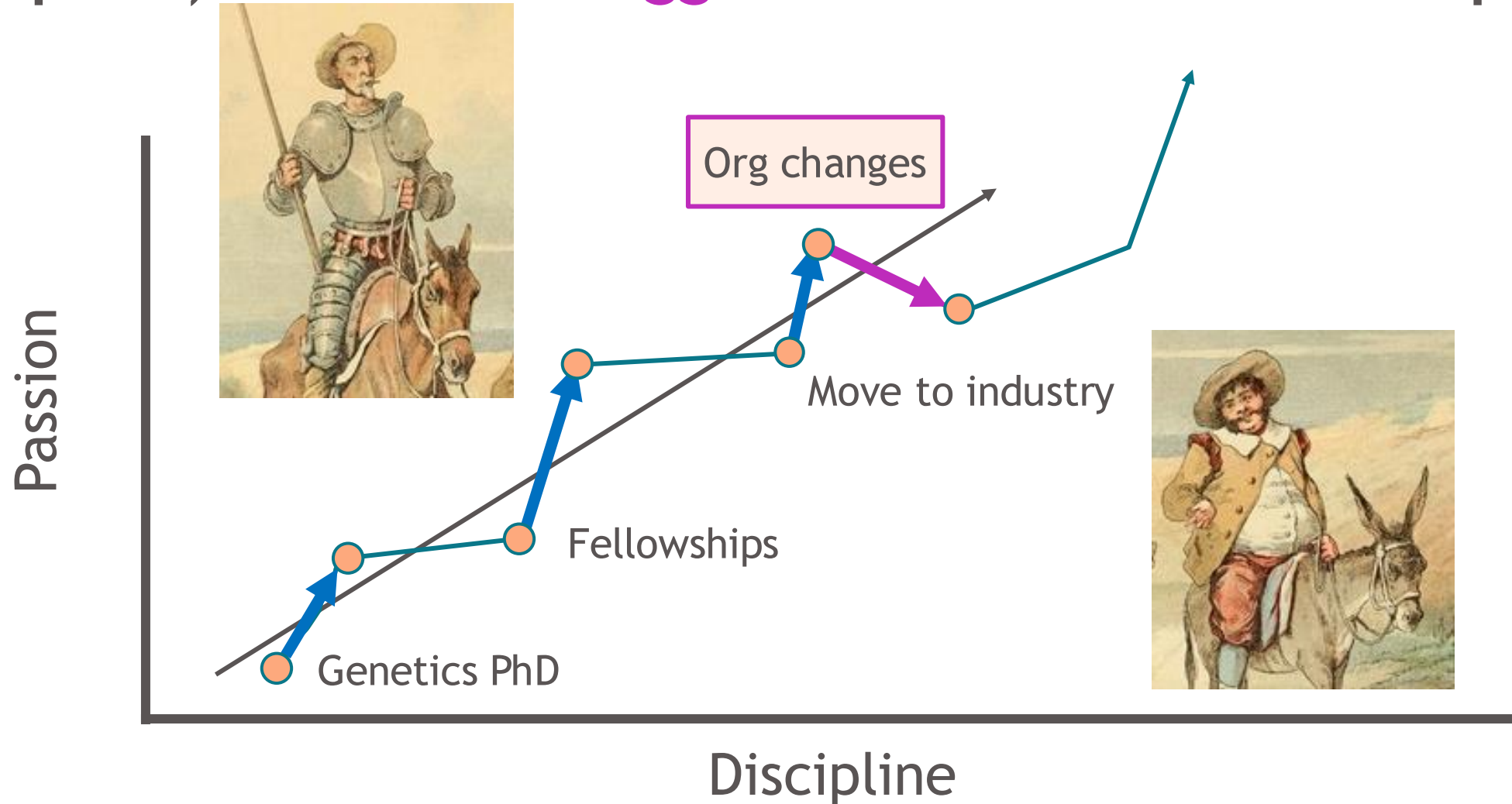
Enter discipline - practical implementation - which ensures dreams get implemented...



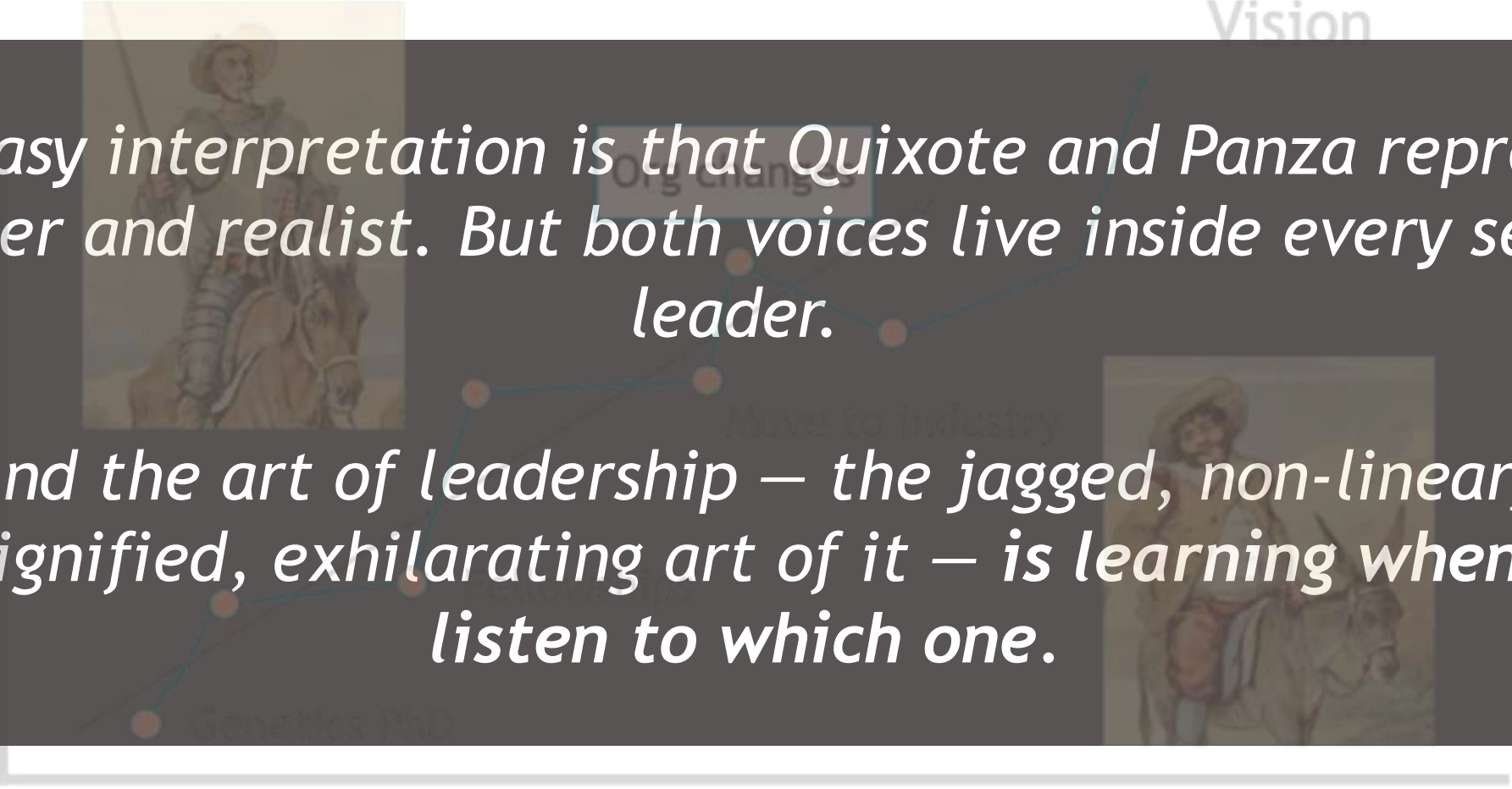
Enter discipline - practical implementation - which ensures dreams get implemented...*with natural tension*



Together, the two voices of Quixote (passion) and Panza (discipline) create the **Jagged Line** of career development



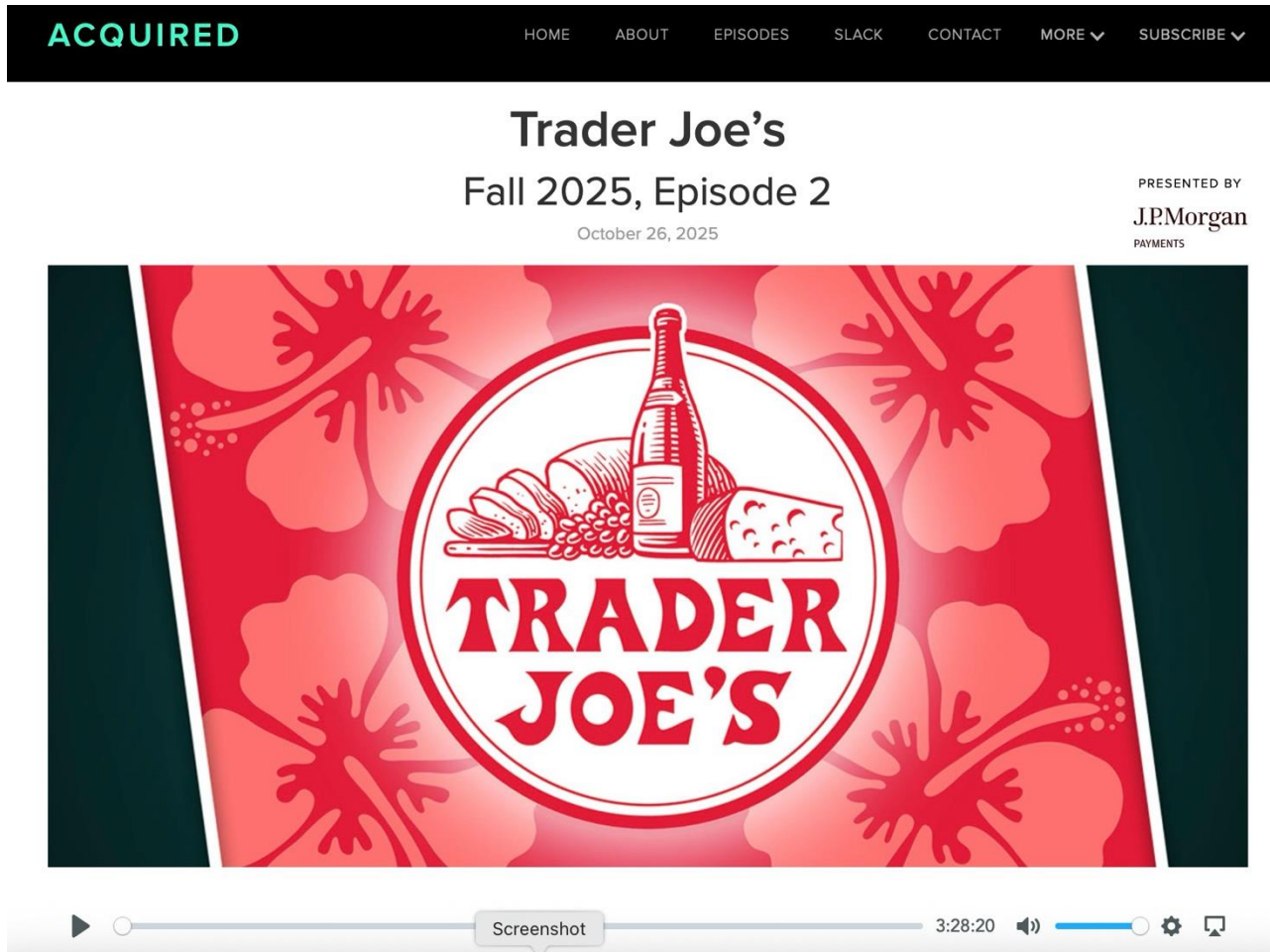
The jagged line of career development



The easy interpretation is that Quixote and Panza represent dreamer and realist. But both voices live inside every serious leader.

And the art of leadership – the jagged, non-linear, undignified, exhilarating art of it – is learning when to listen to which one.

There are many stories of the tension between idealism and reality



Before becoming Trader Joe's, Coulombe ran 7-Eleven knock-off stores called Pronto Markets. When 7-Eleven came to California, he pivoted to:

- Hard liquor

Coulombe looked out 3-5 years and spotted two massive trends:

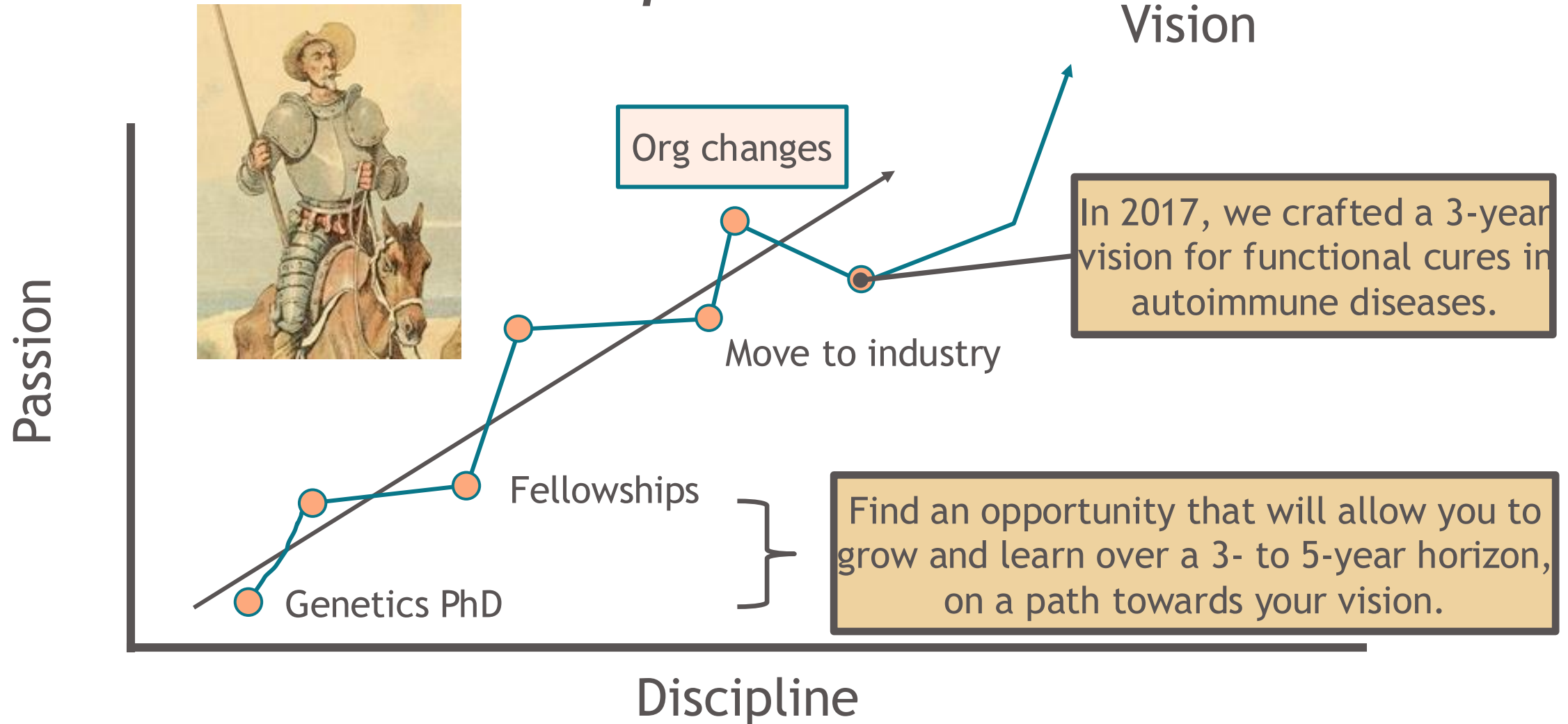
- College education (from 2% to 60%)
- International travel (Boeing 747)

He recognized this would change market dynamics, and he created a new brand of store that sold:

- *Cocktails, not just liquor*

Trader Joe's was born!

The upside of the jagged line: *create quantum units for your own individual development*



Manifestly important and nearly impossible: *what if we could achieve functional cures in autoimmunity?*

nature reviews drug discovery

<https://doi.org/10.1038/s41573-024-00959-8>

Review article

Check for updates

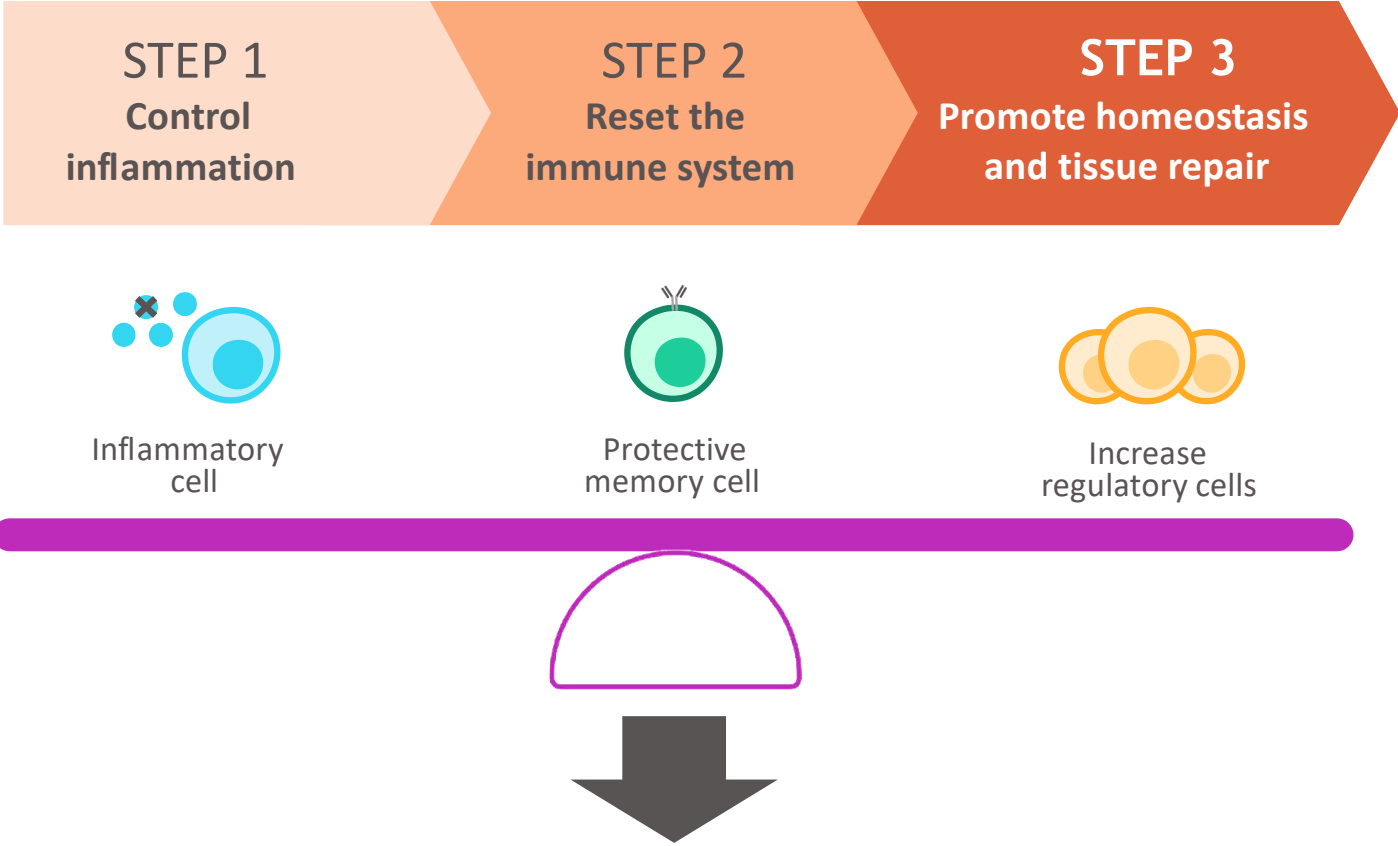
Sequential immunotherapy: towards cures for autoimmunity

Francisco Ramírez-Valle, Joseph C. Maranville, Sophie Roy & Robert M. Plenge

Abstract

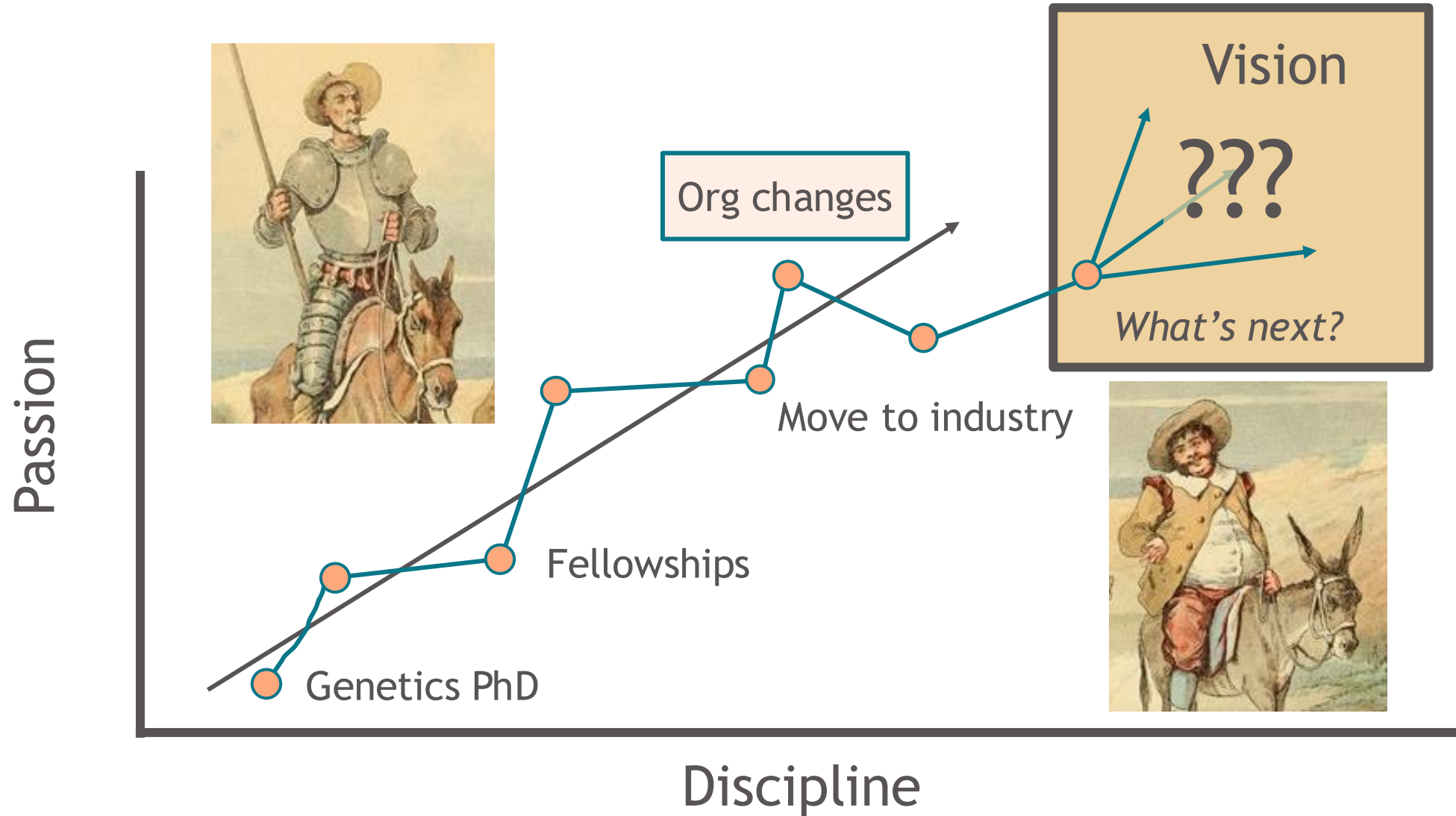
Despite major progress in the treatment of autoimmune diseases in the past two decades, most therapies do not cure disease and can be associated with increased risk of infection through broad suppression of the immune system. However, advances in understanding the causes of autoimmune disease and clinical data from novel therapeutic modalities such as chimeric antigen receptor T cell therapies provide evidence that it may be possible to re-establish immune homeostasis and, potentially, prolong remission or even cure autoimmune diseases. Here, we propose a ‘sequential immunotherapy’ framework for immune system modulation to help achieve this ambitious goal. This framework encompasses three steps: controlling inflammation; resetting the immune system through elimination of pathogenic immune memory cells; and promoting and maintaining immune homeostasis via immune regulatory agents and tissue repair. We discuss existing drugs and those in development for each of the three steps. We also highlight the importance of causal human biology in identifying and prioritizing novel immunotherapeutic strategies as well as informing their application in specific patient subsets, enabling precision medicine approaches that have the potential to transform clinical care.

Sections
Introduction
The potential to cure autoimmune diseases
Step 1: control inflammation
Step 2: reset the immune system
Step 3: homeostasis and tissue repair
Unlocking causal human biology
Conclusions



We started towards this vision in 2017 and submitted a therapeutic concept to the FDA in 2021. We were not sufficiently persistent until 2023 when (stay tuned...)

What is my next ~3-year journey?



What's next? Unfortunately, the **manifestly important and nearly impossible problem** statement remains

Biopharma R&D is...



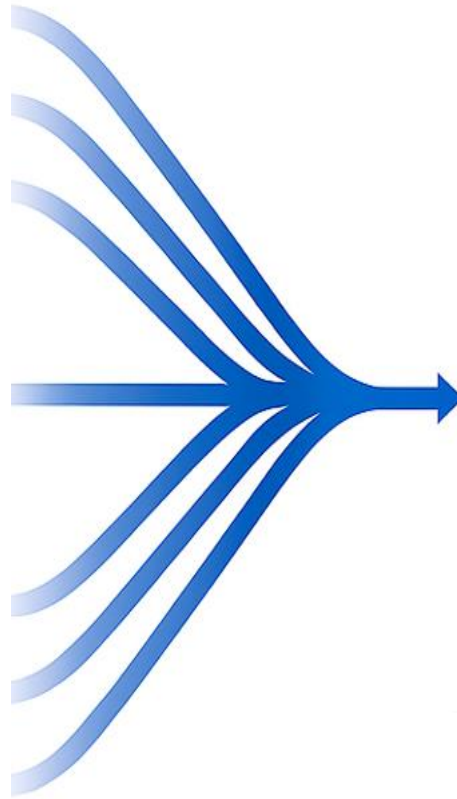
Failure-prone



Expensive



Inefficient



We can solve this by...

- Adhering to rigorous **R&D principles** grounded in causal human biology
- Integrating **AI and automation** to improve efficiency, shorten decision cycles, and enhance the quality of IND output

BMS end-to-end **R&D principles** to achieve top-tier R&D productivity

Causal human biology

Rigorous target validation rooted in human data for patients with high unmet need

Matching modality to mechanism

High-quality therapeutics that match modalities to molecular MoAs, powered by AI/ML

Path to clinical proof-of-concept

Disciplined decision-making in early dev. through targeted patient and endpoint selection

Accelerated full development

Accelerate high-quality development to change practice of medicine at time of launch¹

Maximize Market Access

Market access and commercial excellence to deliver on transformative potential globally

We apply these principles to (1) advance high-quality programs with transformational potential and increased PoS in clinical development; (2) minimize misalignment across the R&D continuum; and (3) enable decision-making by creating a common language to evaluate and prioritize programs.

1. Indication expansion should adhere to same basic principles and considered in the context of LCM value opportunity with agreed ROI

CD19 cell therapy approaches to induce immune reset in multiple autoimmune disease indications



Causal
human biology

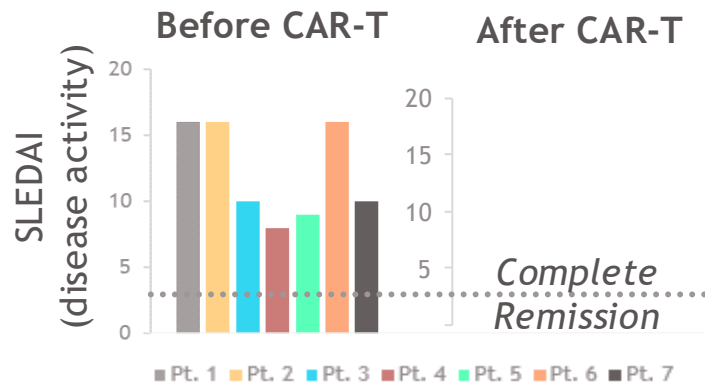


Matching modality
to mechanism

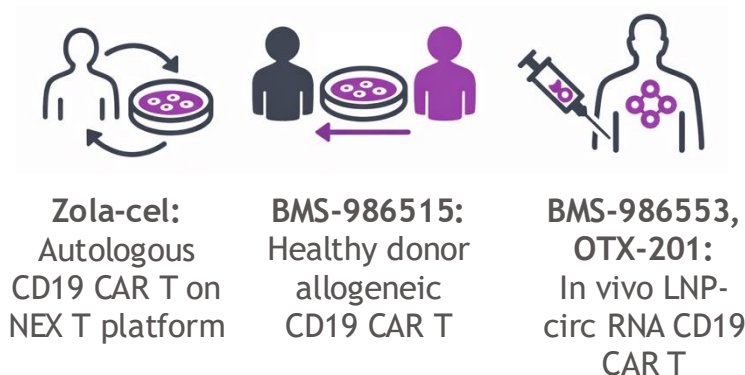


Path to clinical
proof-of-concept

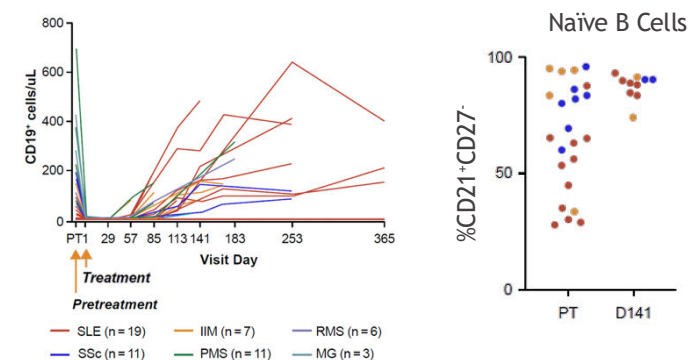
Academic study of CD19 CAR T:
B cell memory reset and
functional cure in SLE



Autologous, allogeneic & in
vivo programs to induce
immune reset



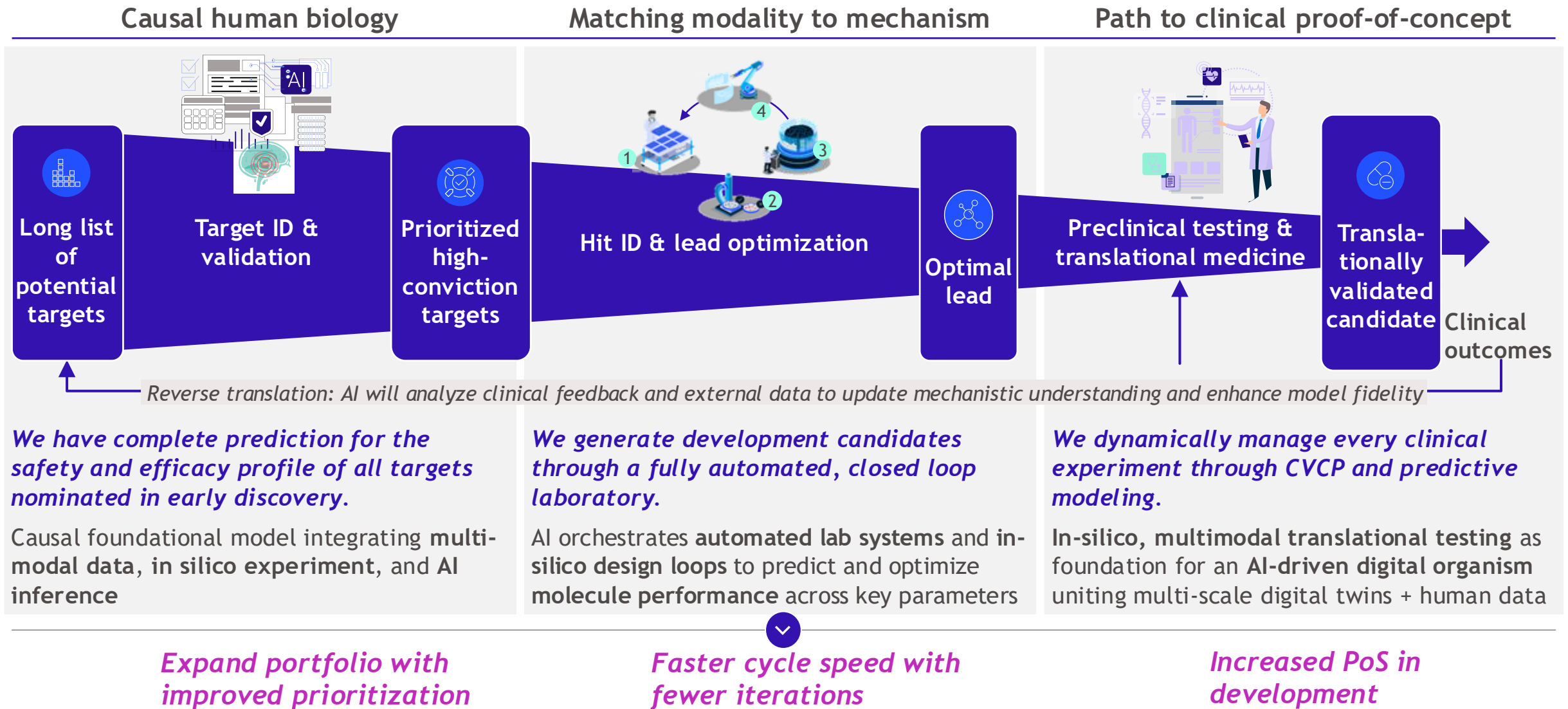
Zola-cel: robust B cell depletion
with recovery of naïve B cells
across AID indications



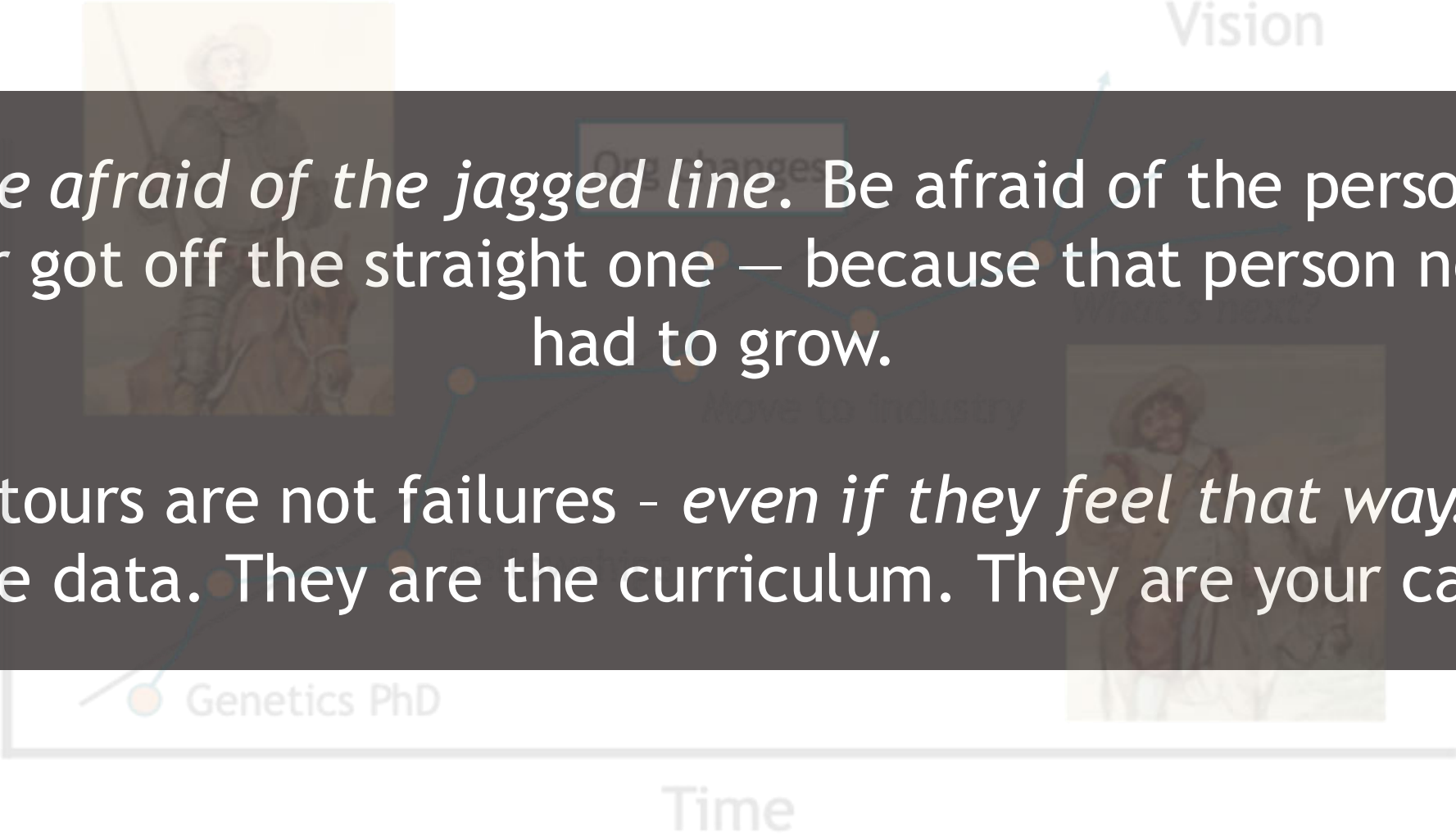
Zola-cel pivotal trials underway in SLE and SSc, HD Allo Ph1 enrolling, and
CD19 in vivo CAR T IND planned for 2026



A new manifestly important and nearly impossible problem has emerged: an **AI-enabled research organization** of the future



The jagged line of career development



Don't be afraid of the jagged line. Be afraid of the person who never got off the straight one — because that person never had to grow.

The detours are not failures - *even if they feel that way.* They are the data. They are the curriculum. They are your career.

Summary

- **My experiences - and lessons learned**
 - Beware of the “personal narrative”
 - Challenge your assumptions
 - Be curious, be courageous, and go deep
 - Ask big questions - manifestly important, nearly impossible
 - Embrace a jagged line in career development
- **What's next**
 - End-to-end R&D principles
 - Functional cures in autoimmunity
 - Artificial Intelligence (AI)