



Clinical Stage Drug Development Platform
Developing Therapeutics
for GI, Mucosal and Immunological Diseases

September, 2014



Executive Summary

- Biopharmaceutical company founded in 2006, based in Ghent, Belgium
- Experienced team (22 employees) with all key competencies available
- Unique & proprietary platform: ActoBiotics™
 - ORAL administration & mucosal delivery of biologics: safe, efficacious & cost-effective
 - Wide product range with clinical POC validation, phase 2 stage
 - High medical need indications: Crohn's disease, cancer supportive care, diabetes...
- Recently completed P1 trial: unequivocal evidence of high exposure to live bacteria and certolizumab in the human GI tract
- Validating deals: Stallergenes / MSD
- Extensive IP estate

Key Pipeline & Financial Milestones

Pipeline & Collaborations

- AG013 - positive phase 1B results in mucositis, phase 2-ready
 - Active out-licensing process
- AG014 – Oral anti-TNF α phase 1B/2A-ready; data in IBD by 1H/2016
- Extensive preclinical portfolio of products
 - Collaboration agreements: in progress
- Agreements with Merck (antibody expression) & Stallergenes (oral allergy)

Financial

- Series A and B financing rounds: € 46 million
 - Gimv, LSP, Ventech, Aescap, Biovest, Baekeland, VIB, Saffelberg

Proven Management Team

- Bernard Coulie, MD, PhD, MBA
 - CEO & CMO
 - J&J PRD, Mayo Clinic GI staff
- Emil Pot, LLM
 - General Counsel
 - VIB Tech Transfer
- Lothar Steidler, PhD
 - VP Technology
 - Inventor, VIB Principal investigator
- Magda Van Hijfte, MSc
 - Director Finance & HR
 - Tele Atlas, BASF
- Anjan Aralihalli, MBA
 - CBO
 - Abbott, Sanofi, Shionogi
- Pieter Rottiers, PhD
 - VP R&D
 - VIB Principal Investigator
- Decebal Bora, PharmD
 - Director Regulatory Affairs
 - Roche, Biogen-Idec, Baxter
- Sam Corveleyn, PharmD, PhD
 - Director CMC Operations
 - Nycomed

Board of Directors

- Staf Van Reet, PhD
 - Chairman and Independent Director
- Patrick Van Beneden
 - Gimv (BE)
- Karl Naegler, PhD
 - Gimv (BE)
- Anne Portwich, PhD
 - LSP (NL)
- Mounia Chaoui, PhD
 - Ventech (FR)
- Rudi Mariën
 - Biovest (BE)
- Johan Cardoen, PhD
 - VIB (BE)
- Dinko Valerio, PhD
 - Aescap (NL)
- Jos Sluys
 - Saffelberg Investments (BE)
- Bernard Coulie
 - CEO, ActoGeniX

Scientific Advisory Board

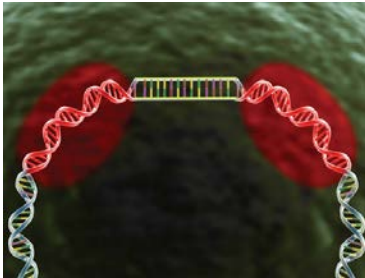
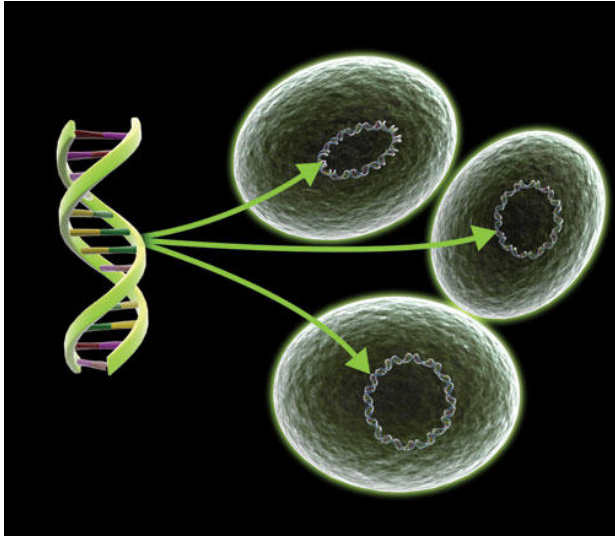
- William J. Sandborn, MD
 - Professor of Medicine,
 - Chief of Gastroenterology, UC San Diego
- Brian Feagan, MD
 - Professor, U. of Western Ontario (Canada)
 - Director, Robarts Research Institute
- Stephen Sonis, DMD, DMSc
 - Professor, Oral Medicine, Infection & Immunity, Harvard Medical School
 - Chief, Oral & Maxillofacial Surgery & Dentistry, Brigham & Women's Hospital (Boston)
- Wesley Burk, MD
 - Curnen Distinguished Professor and Chair of the Department of Pediatrics at the University of North Carolina School of Medicine
 - Physician in Chief at N.C. Children's Hospital
- Séverine Vermeiren, MD, PhD
 - Professor of Medicine, U. of Leuven
 - Division of Gastroenterology
- Chantal Mathieu, MD, PhD
 - Professor of Medicine, U. of Leuven
 - Chief of Endocrinology
- Paul Rutgeerts, MD, PhD
 - Professor of Medicine, U. of Leuven

The Concept of ActoBiotics™

- Oral administration and delivery of bio-therapeutics to the GI tract based on *local synthesis*
- *Local* synthesis carried out by safe, living, lactic acid bacteria administered to the patient
- *Lactococcus lactis* is genetically engineered to locally secrete bio-therapeutics such as cytokines, antibodies, hormones,...
- *Lactococcus lactis* is not part of oral or GI microflora and does not replicate in the oral cavity or GI tract
- Potential to use platform for targeted modulation of the Microbiome

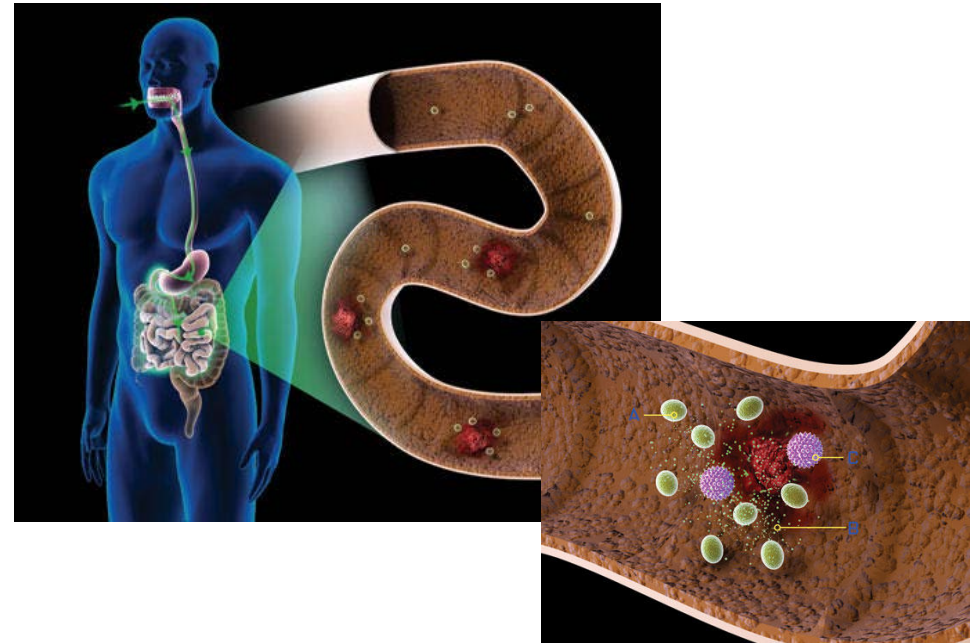
The Concept of ActoBiotics™

Genetic engineering of *Lactococcus* to create an ActoBiotic™ by chromosomal insertion of one or multiple genes



Containment system preventing survival of excreted bacteria outside of the human body

Coated capsules with freeze-dried Actobiotic™ are taken orally by patient



ActoBiotic™ released in gut and locally secreting therapeutic at site of disease

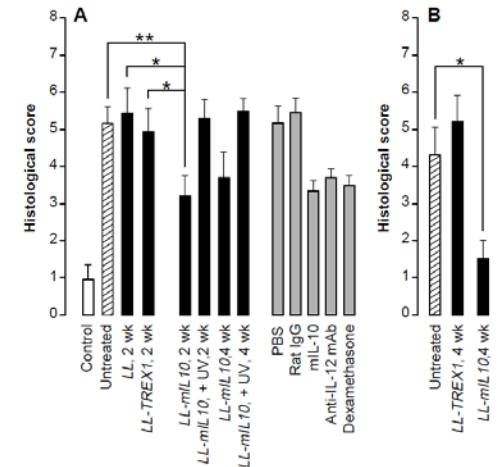
Initial POC Published in Prestigious Journals



Treatment of Murine Colitis by *Lactococcus lactis* Secreting Interleukin-10

Lothar Steidler,^{1*}† Wolfgang Hans,^{1†} Lieven Schotte,¹
Sabine Neirynck,¹ Florian Obermeier,² Werner Falk,²
Walter Fiers,¹ Erik Remaut¹

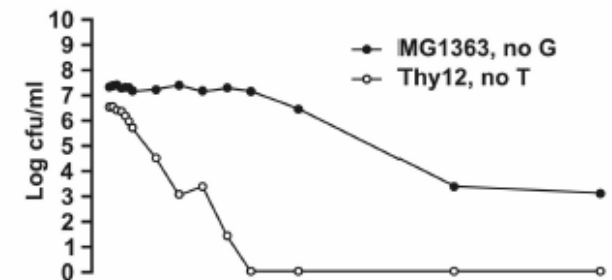
25 AUGUST 2000 VOL 289 SCIENCE



**nature
biotechnology**

Biological containment of genetically modified *Lactococcus lactis* for intestinal delivery of human interleukin 10

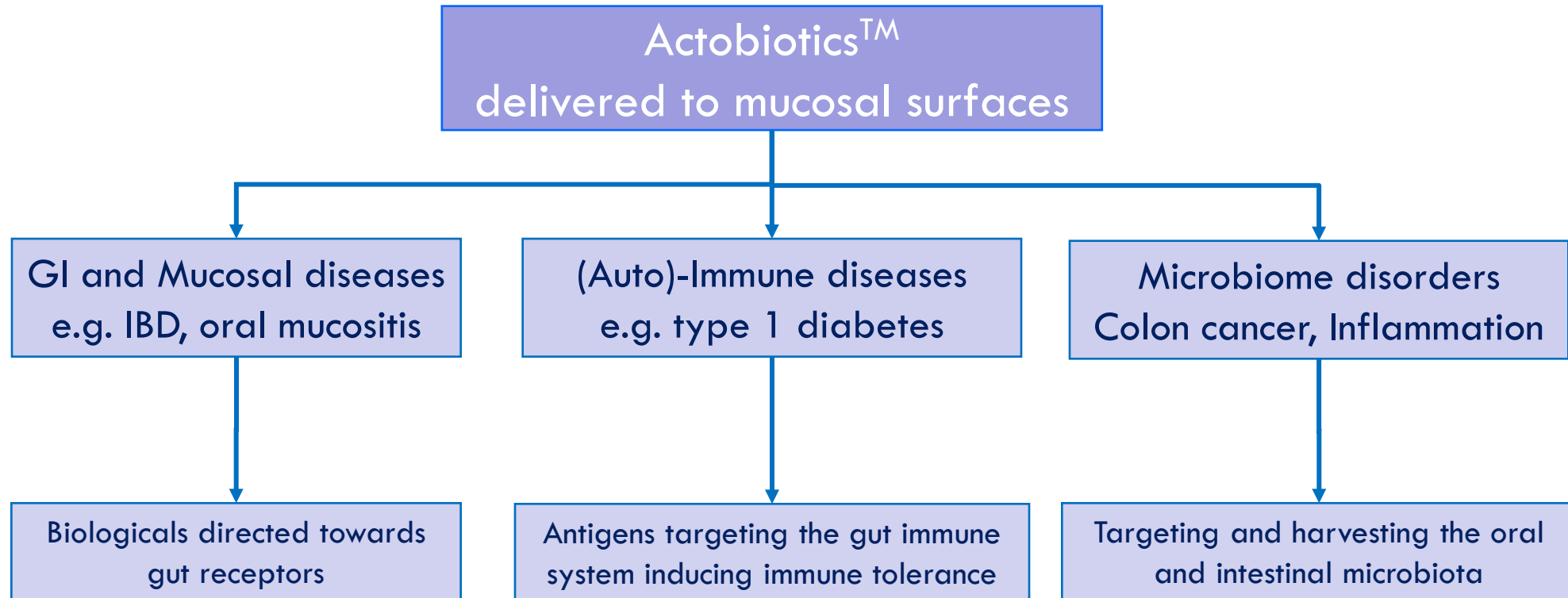
Lothar Steidler¹, Sabine Neirynck¹, Nathalie Huyghebaert², Veerle Snoeck³, An Vermeire², Bruno Goddeeris³,
Eric Cox³, Jean Paul Remon² & Erik Remaut¹



NATURE BIOTECHNOLOGY VOLUME 21 NUMBER 7 JULY 2003

ActoBiotics™

Mucosal diseases, Auto-immune disorders, Microbiome disorders



ActoBiotics™ – Key Advantages Over Current Biologics

ActoBiotics™

- Oral administration
- No toxicity or immunogenicity
- Local mucosal delivery at site of inflammation: optimal tissue availability
- Multiple proteins in single product
- Very low cost of goods, pricing flexibility: € 0,5/capsule

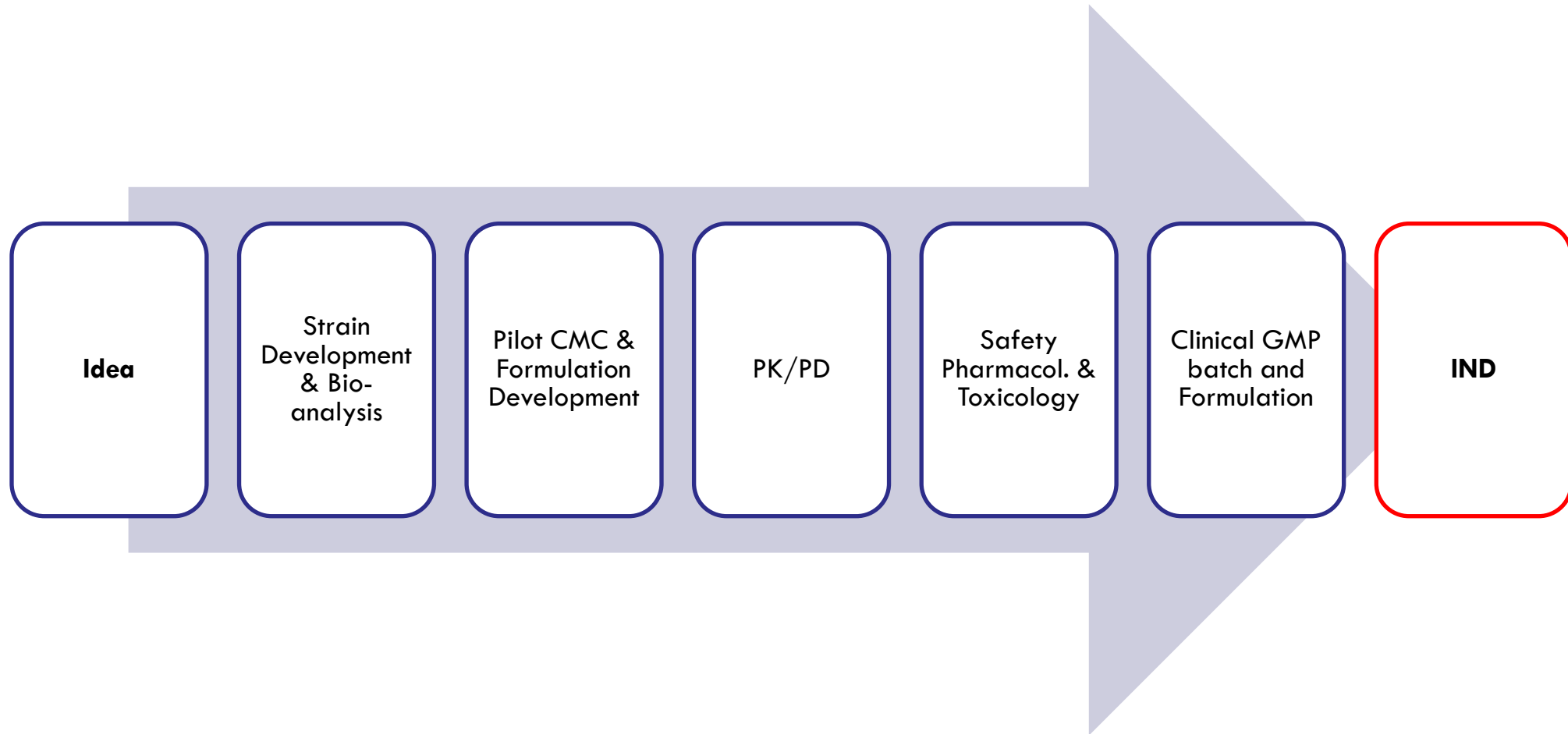


Classic Biologics

- Systemic administration
- Systemic toxicity, immunogenicity
- Limited tissue penetration, notably in the gut
- Single protein
- High Cost of Goods, high price



From Idea to IND in < 18 months



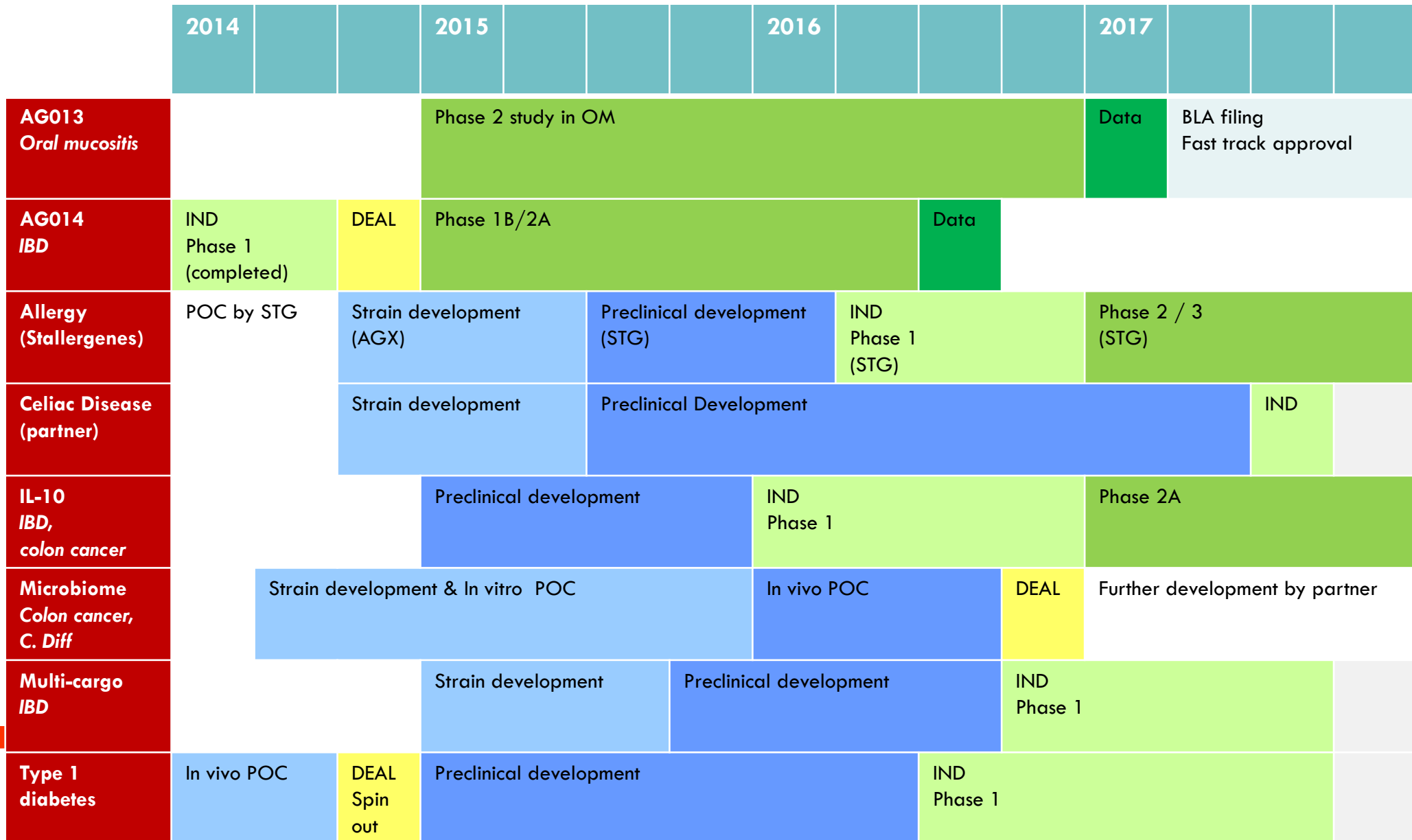
Development, Regulatory and Production established

- Preclinical & clinical development established
 - Safety & tolerability confirmed in preclinical & clinical studies
- Regulatory path cleared in US and EU
 - Clear understanding of requirements, processes & timelines
 - Successful IND/CTA filings
- Production process
 - Efficient & reliable cGMP manufacturing process established
 - Current manufacturing capacity already sufficient for commercial supply
 - Product stable at 2-8 °C up for at least **4 yrs**

ActoBiotics™ - Strong and Dominant IP

- Patent portfolio covering platform and specific applications
 - 147 granted & 56 pending patent applications covering principle of ActoBiotics™, technology platform, production process & various therapeutic uses
- Broad claims granted in US, EU, Japan & China
- Opportunities to create novel IP for existing protein drugs

ActoBiotics™ - Pipeline Development



AG014 – *L. Lactis* Secreting Anti-TNF α Fab for IBD

AG014 in Inflammatory Bowel Diseases

- *L. Lactis* delivering anti-TNF α Fab (certolizumab)
- Targeted delivery of anti-TNF α in inflamed tissues
 - Superior tolerability and safety profile vs injectable anti-TNF α
 - More convenient dosing (oral capsules) – better patient compliance
 - Pricing flexibility vs injectable anti-TNF α
 - ActoBiotics™ can be positioned as 1st or 2nd line therapy in IBD
- Phase 1 PK study in HV finalized
- Phase 1B/2A study in IBD patients starts in 2015, data expected by 1H/2016



Crohn's disease

ActoBiotics™ – Market Overview

IBD Market

- ActoBiotics™ can limit/replace/delay use of therapies such as steroids, systemic anti-TNF α mAbs, or immunosuppressants in IBD
- Potential market in IBD for an effective oral treatment is \$2-3B US*
- AG014
 - Potential for first or second line therapy (safety, efficacy, pricing flexibility)
 - Validated target

* Internal Market Research (oral therapy & TPP)

Positioning in 2020 Market

Mild to Moderate Crohn

AG014 as first line vs steroids/immunosuppressants

Severe Crohn

Anti-TNF α (biosimilars)
Novel MoAs in anti-TNF α non-responders

Mild to Moderate UC

AG014 as 2nd line after 5-ASA vs steroids/immunosuppressants

Severe UC

Anti-TNF α (biosimilars)
Novel MoAs in anti-TNF α non-responders

AG014 in IBD – Preclinical Data

Initial proof of concept established in colitis models

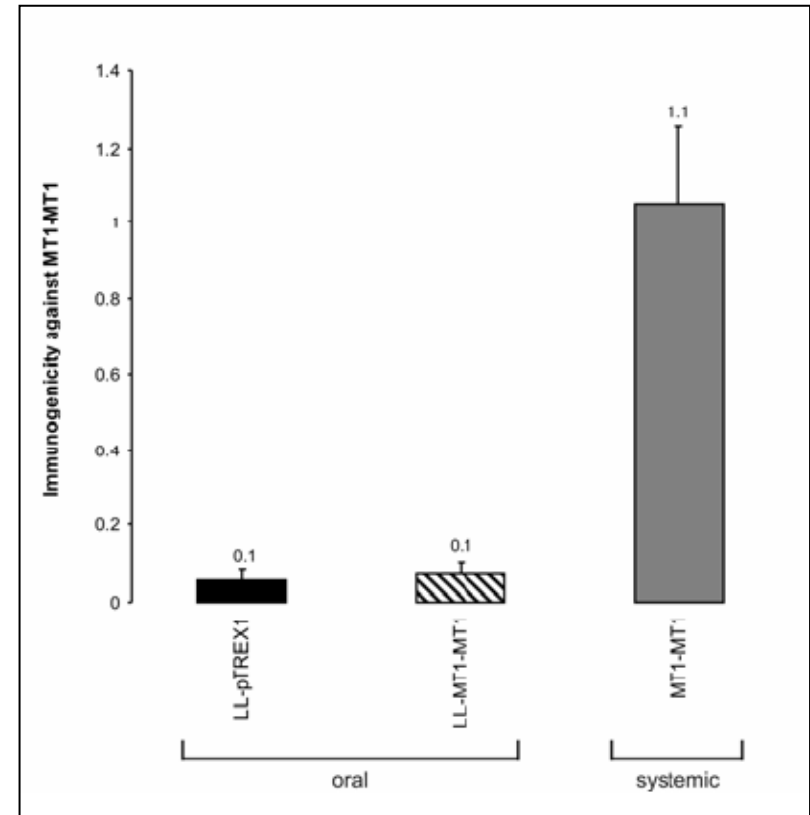
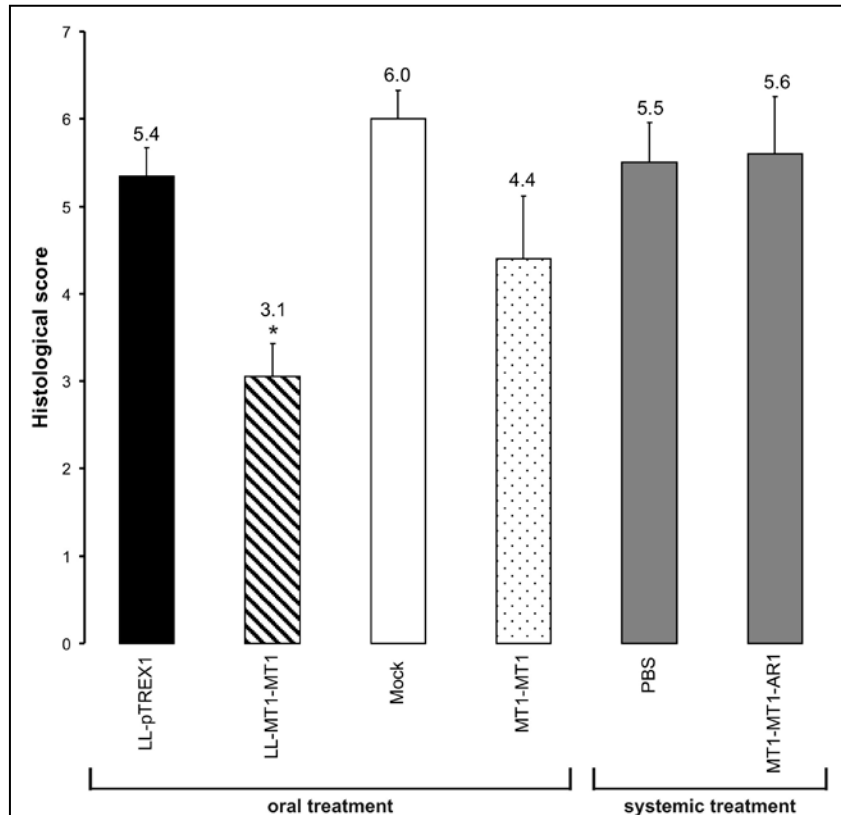
Orally administered *L. lactis* secreting an anti-TNF Nanobody demonstrate efficacy in chronic colitis

K Vandenbroucke^{1,2,3}, H de Haard⁴, E Beirnaert⁴, T Dreier⁴, M Lauwereys⁴, L Huyck^{1,2}, J Van Huysse⁵, P Demetter⁶, L Steidler³, E Remaut^{1,2}, C Cuvelier⁵ and P Rottiers^{1,2,3}

Novel, bile-resistant strain expressing certolizumab has completed preclinical development (PK, tox) towards CTA and IND filing in 2014 for the conduct of a HV study & Phase 2A study respectively

AG014 - anti-mTNF α antibody (POC)

Superior efficacy without causing immunogenicity



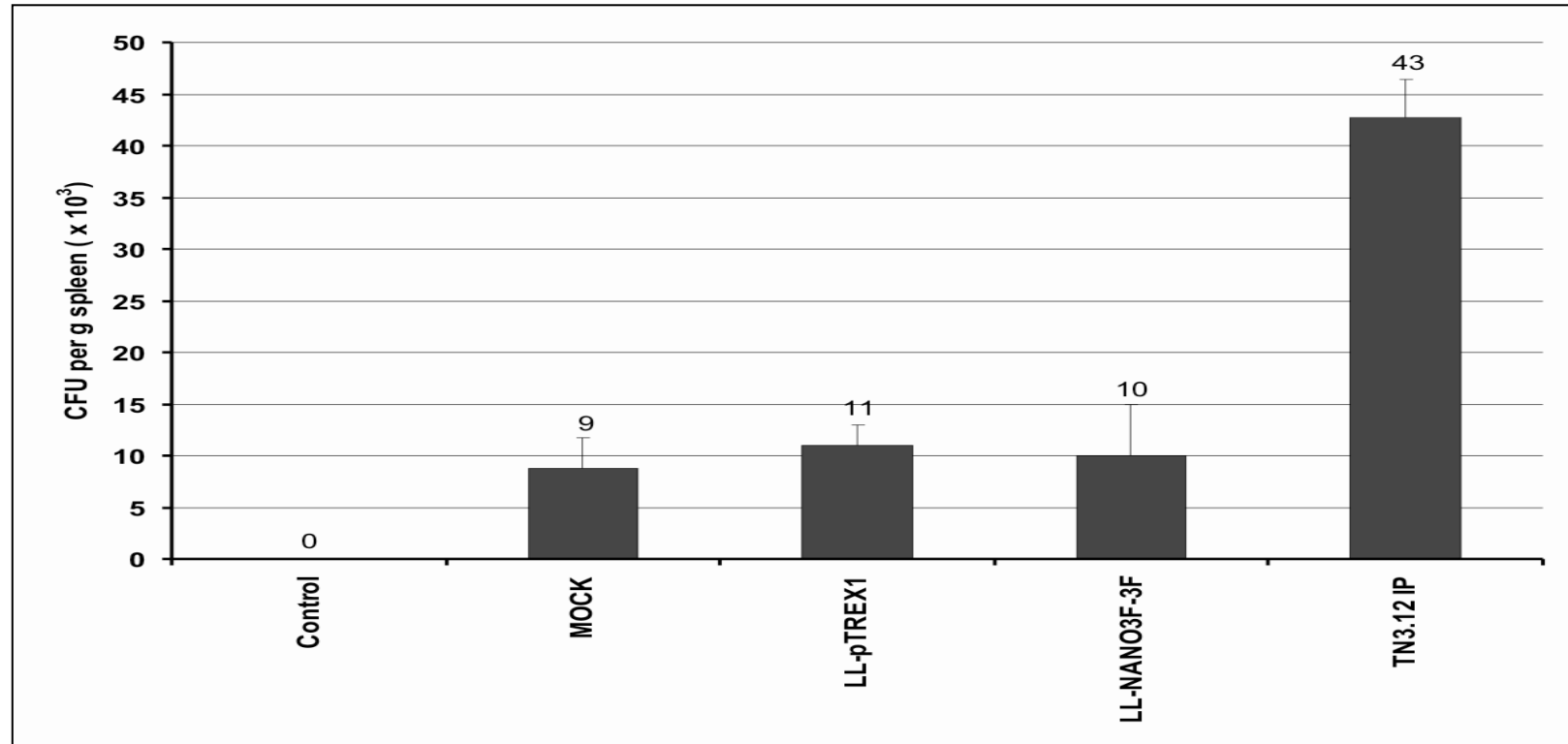
Comparison between anti-TNF α secreting *L. lactis* and purified anti-TNF α (oral and systemic) in terms of efficacy and immunogenicity in established chronic enterocolitis

LL-pTRES1: *L. lactis* empty vector control, LL-MT1-MT1: *L. lactis*-secreting anti-mTNF α ;

MT1-MT1(-AR1): purified anti-mTNF α (50mg/kg oral; 25mg/kg systemic)

AG014 - anti-mTNF α antibody (safety)

No risk for opportunistic infection vs systemic anti-TNF α (Salmonella infection model)

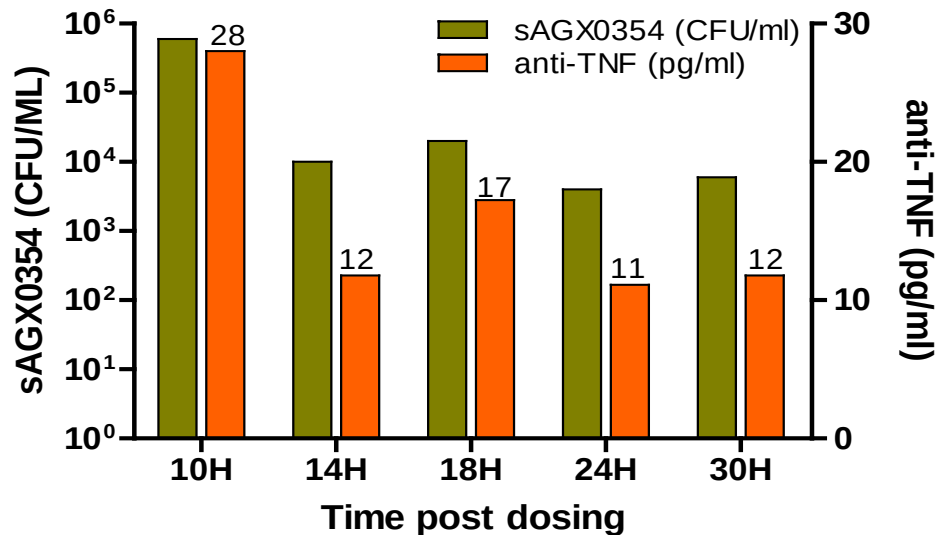


Salmonella enterica 5×10^4 CFU iv; 7 day treatment

AG014 – Pig PK studies

Prolonged exposure (30hrs) to *L. lactis* and certolizumab after capsule administration

sAGX0354 and certolizumab recovered
from pig caecum luminal content
(Spearman correlation $P < 0.05$)



- Significant correlation between recovery of sAGX0354 and certolizumab in the caecum luminal content (Figure)
- Exposure of sAGX0354 and certolizumab is high in the proximal colon at 10H post dosing corresponding to values recovered in fistulated pigs
- Recovery after inspiking in fresh luminal content 20-30%

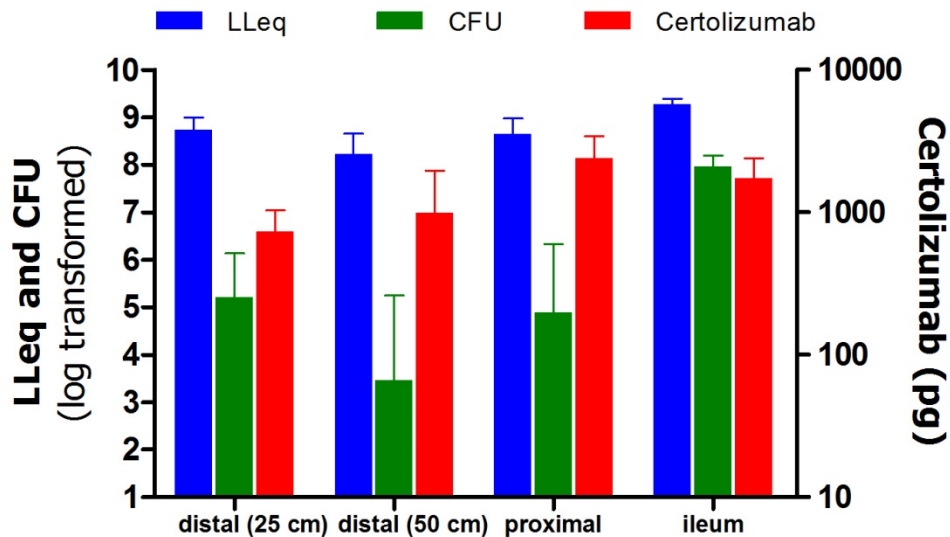
AG014 – Summary preclinical

- AG014: high expression levels of certolizumab
 - In vitro hTNF neutralization capacity
 - In vitro bile resistance
- Pharmacodynamic studies demonstrated efficacy in colitis models
 - Reduction of mortality, inflammation & normalisation of mucosal inflammatory cytokines/chemokines
- PK and safety pharmacology in animal models
 - Continued colonic exposure to *L. lactis* & certolizumab upto 30 hrs after administration
 - No safety issues
- Repeat Dose Toxicity study: no drug-related findings

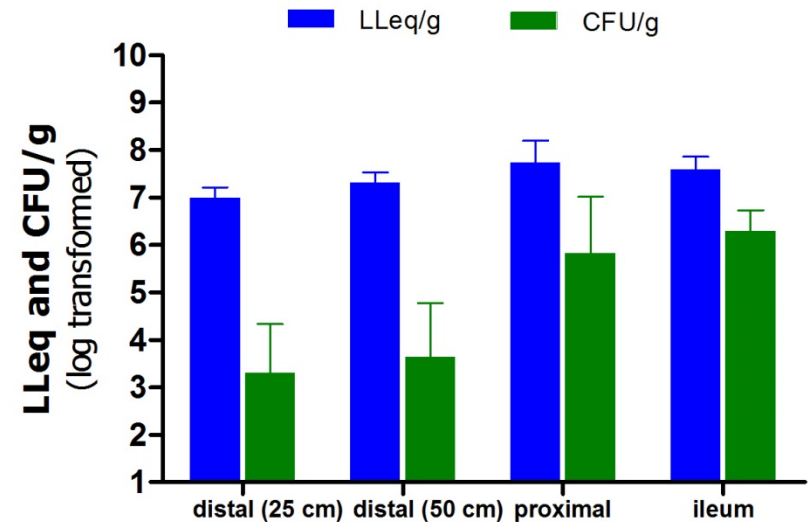
AG014 – Human PK studies

Prolonged exposure to *L. lactis* and certolizumab after capsule administration

Luminal content collected during full colonoscopy
AG014 bacteria (live and total) and certolizumab per sample



Biopsies taken during full colonoscopy
AG014 bacteria (live and total)



AG014 – Development - Timelines

- RAC recommendation obtained (December 2013)
- IND approved (April 2014)
- Phase 1 PK study (Belgium): completed
 - Data set provides unequivocal evidence of high exposure to live bacteria and certolizumab in the human GI tract
 - Live bacteria and certolizumab were measured in all relevant GI regions (ileum, pan-colonic)
 - No systemic absorption of bacteria or certolizumab
- Phase 1B/2A (US): start 2015, (PI: W Sandborn)
 - Moderate to severe UC
 - Safety, tolerability / PK / Exploratory efficacy

AG013 – Next Generation Product Candidate for Oral Mucositis

AG013 in Oral Mucositis – An Unmet Medical Need

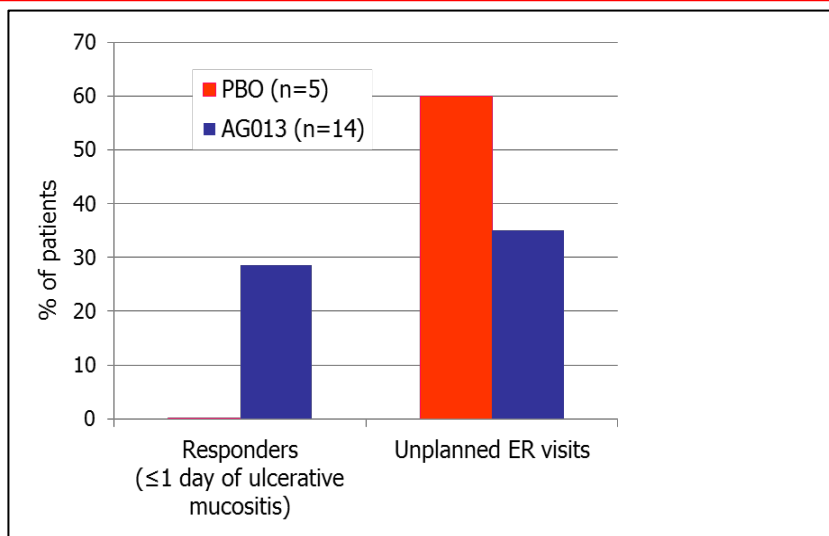
- Oral mucositis: painful necrosis & ulceration of the mucosa in the oral cavity due to chemoradiation
- > 95% of Head & Neck Cancer patients undergoing chemoradiation treatment suffer from oral mucositis*
- ~40% of all chemotherapy patients suffer from oral mucositis**
- Huge unmet medical need:
 - Existing therapies are not drugs (e.g., bioadhesives), or provide limited efficacy, serious safety concerns and are inconvenient (infusion therapy)
 - # Cancer patients will increase from 12.8MM in 2008 to 22.2MM in 2030 (2013 Cancer Progress Report)



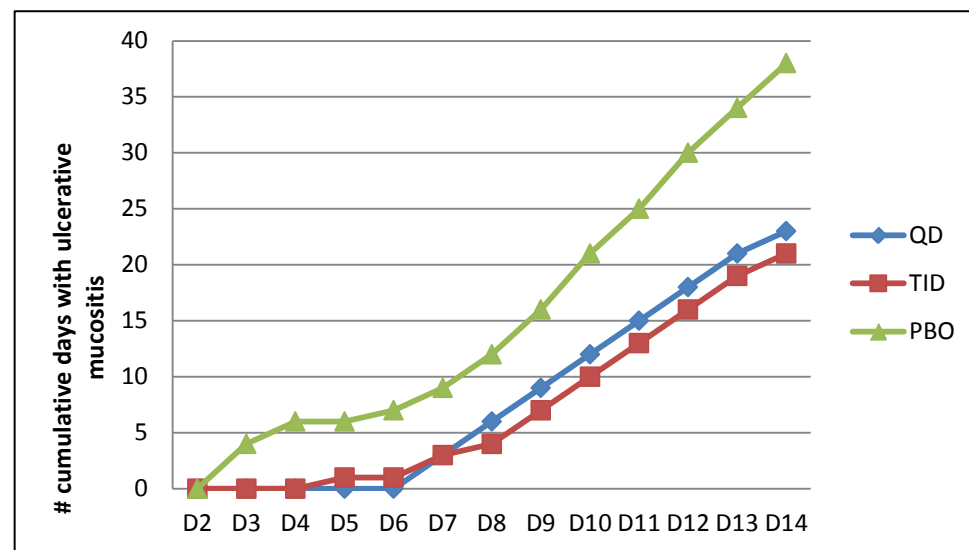
AG013 in Oral Mucositis – Efficacious and safe

- Active principle of AG013: human Trefoil Factor 1 (hTFF1)
- **Orphan Drug** status in EU; **12-Year** BLA exclusivity & **“Fast Track”** eligible (US)
- Is Phase 2B-ready

**29 % of AG013 treated had ≤ 1 day of UOM* vs placebo treated had >2 days;
AG013 patients had reduced unplanned office & ER visits**



AG013 reduces cumulative days with ulcerative mucositis vs placebo by 40 %



Oral Mucositis - An **attractive** market

- Peak sales could exceed € 700 million

Tumor entity	# patients*	OM incidence**	AG013 market share***	AG013 sales
All cancers (excl. H&N)	15,700,000	5 - 40%	2.5 - 20%	€ 620 MM
H&N cancer	821,000	75 - 95%	5 - 40%	€ 140 MM
Total				€ 760 MM

- Avg; treatment duration of 42 days for H&N & 84 days for other cancers
- Ex-factory price €30 - €60/day or €1,260 - €2,520 (varies by country)
 - MuGard available for \$1,700/course of therapy (Oncology Supply, ASB, Jan 2014)

Immune tolerance programs

Treatment of Auto-immune Diseases by Induction of Antigen-specific Tolerance

- Type 1 Diabetes, Celiac Disease, Allergy

ActoBiotics™ in Allergic Diseases

- Collaboration agreement with Stallergenes: 5 allergens
- Based on oral tolerance induction by local mucosal delivery of allergens/epitopes in the mouth or GI tract
- Major advantages:
 - No need for large-scale purification of human allergens
 - Specific epitope selection, standardization and dosing possible
 - Delivery of single and multiple allergens
 - Co-delivery with a tolerance-enhancing factor (eg IL-10)
 - *L. lactis* modulates dendritic cell function (mucosal adjuvants)

ActoBiotics™ in Type 1 Diabetes

First evidence ever of possible reversal of type 1 diabetes

Reversal of autoimmune diabetes by restoration of antigen-specific tolerance using genetically modified *Lactococcus lactis* in mice

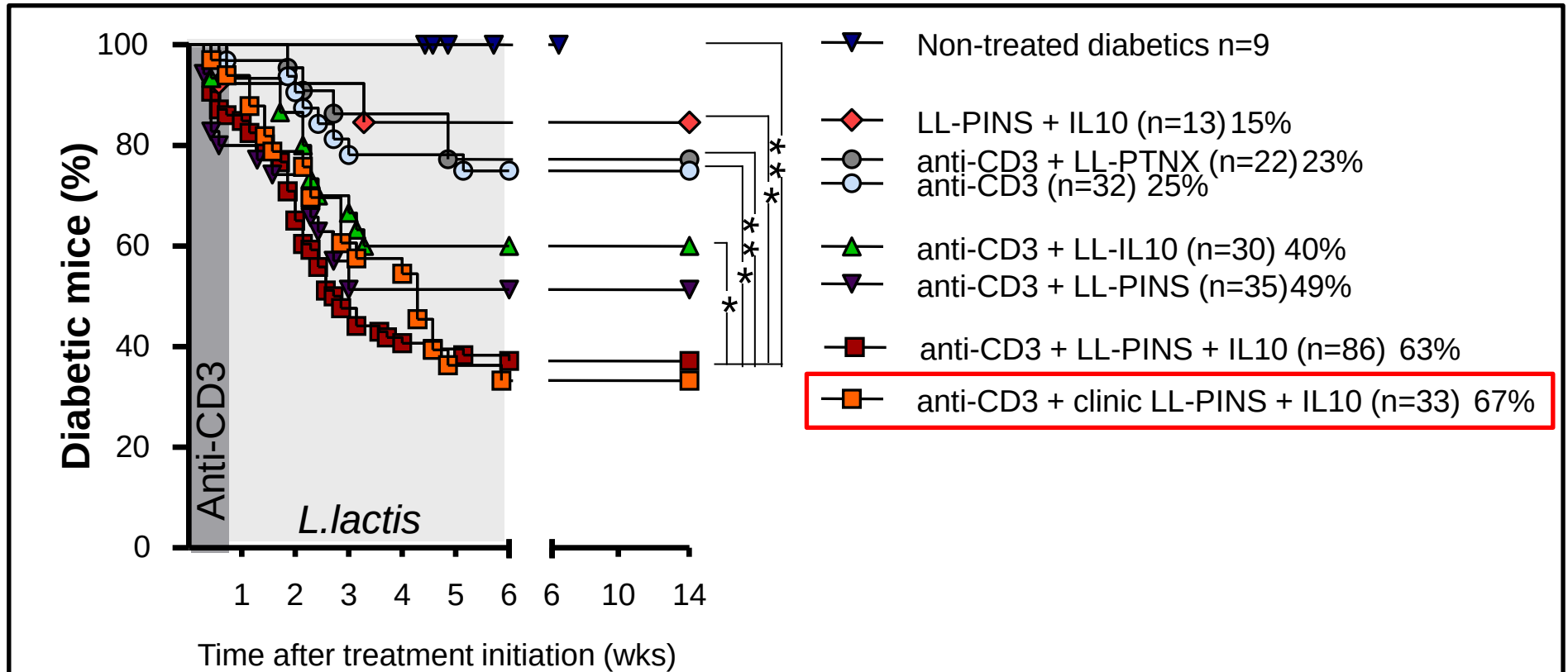
Tatiana Takiishi,¹ Hannelie Korf,¹ Tom L. Van Belle,¹ Sofie Robert,¹ Fabio A. Grieco,²
Silvia Caluwaerts,³ Letizia Galleri,² Isabella Spagnuolo,² Lothar Steidler,³
Karolien Van Huynegem,³ Pieter Demetter,⁴ Clive Wasserfall,⁵ Mark A. Atkinson,⁵
Francesco Dotta,² Pieter Rottiers,³ Conny Gysemans,¹ and Chantal Mathieu¹

¹Clinical and Experimental Endocrinology, KU Leuven, Leuven, Belgium. ²Diabetes Unit, Department of Internal Medicine, Endocrine and Metabolic Sciences and Biochemistry, University of Siena and Fondazione Umberto Di Mario ONLUS, Siena, Italy. ³ActoGeniX NV, Zwijnaarde, Belgium. ⁴Department of Pathology, Université Libre de Bruxelles (ULB), Brussels, Belgium. ⁵Department of Pathology, Immunology and Laboratory Medicine, College of Medicine, University of Florida, Gainesville, Florida, USA.

The Journal of Clinical Investigation <http://www.jci.org>

ActoBiotics™ in Type 1 Diabetes – Antigen-specific Treatment

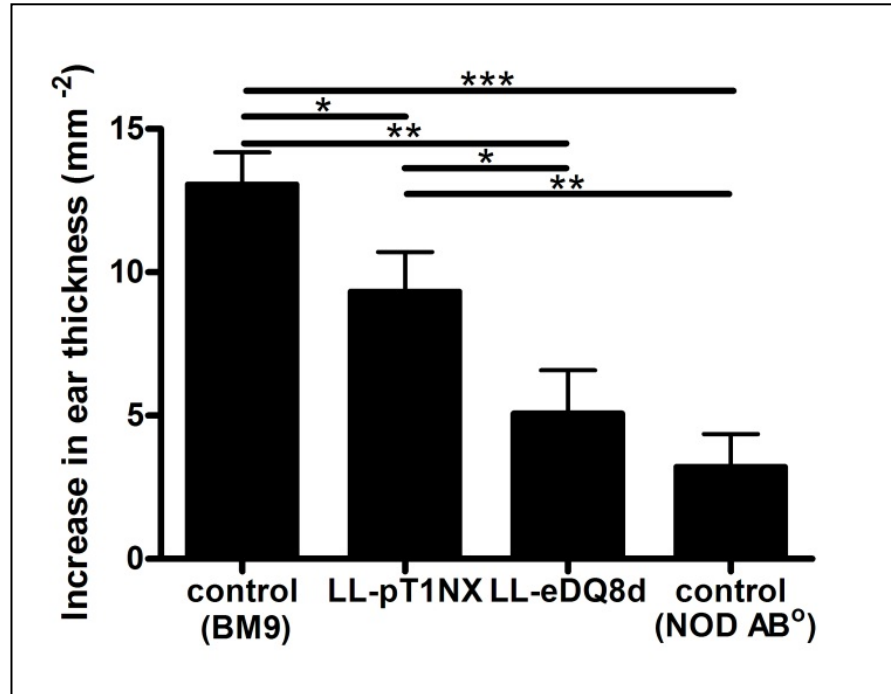
Combination therapy stably reverted autoimmune diabetes in new-onset diabetic mice



- Combination therapy (anti-CD3 + LL-PINS+hIL10) triggers synergistic efficacy and stably reverts overt diabetes in 60-70% of the animals.

ActoBiotics™ in Celiac Disease

Gluten desensitization in Celiac Disease model*



Gluten-specific T cell response is decreased upon oral administration of *L. lactis*-secreting DQ8d gluten epitope.

LL-pT1NX: *L. lactis* empty vector control, LL-eDQ8d: *L. lactis*-secreting gluten DQ8 epitope, control (BM9): vehicle control, control (NOD AB°): non-sensitized control mice

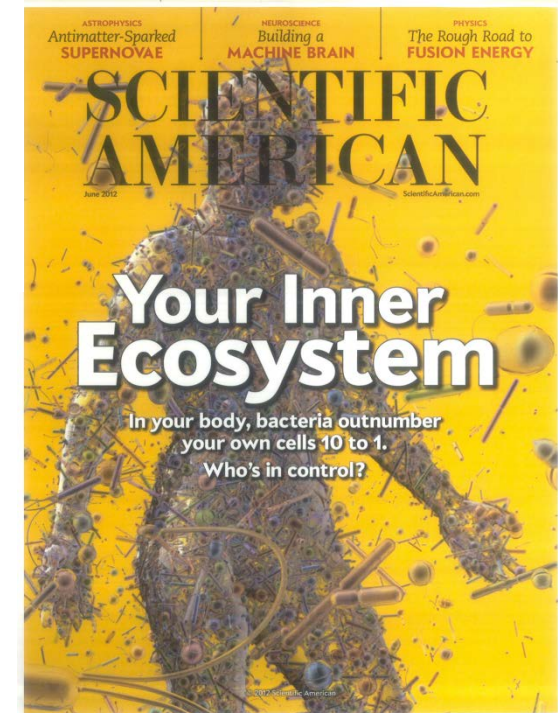
* DQ8 Sensitized NOD ABo DQ8 transgenic mice

Huibregtse et al., J. Immunol 2009

Targeted Microbiome modulation

Human Microbiome

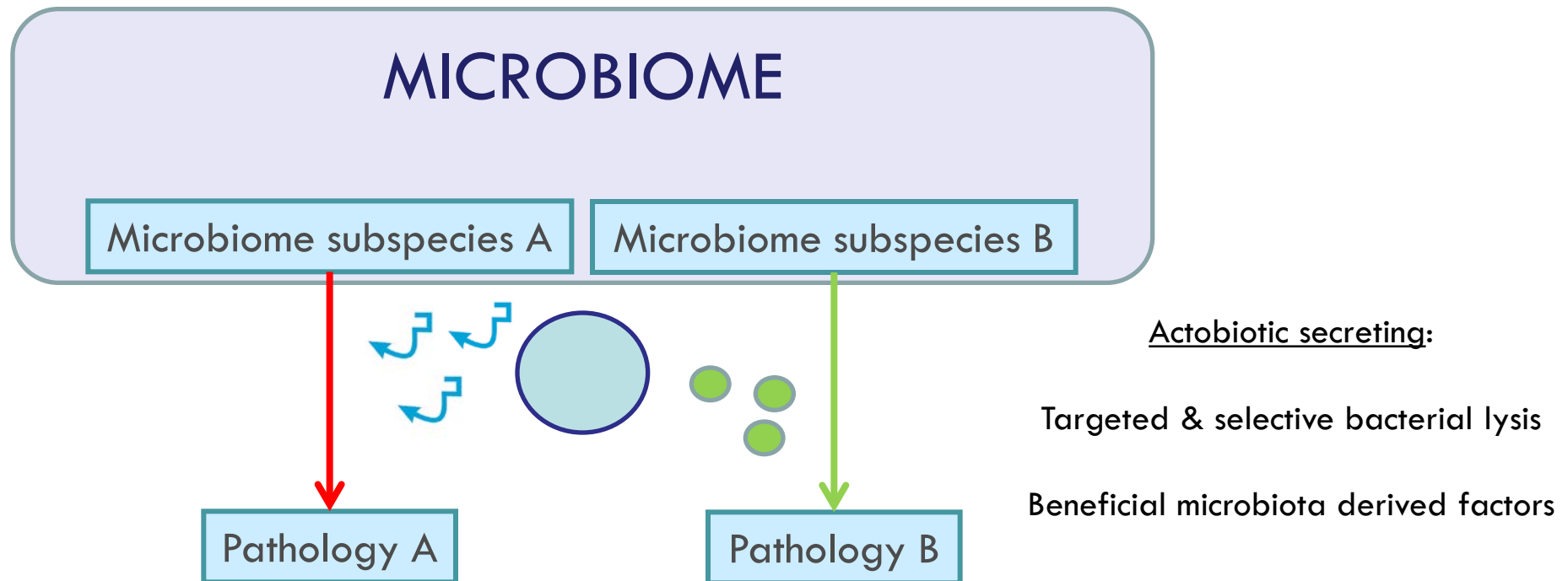
“All Disease Begins In the Gut” - Hippocrates



ActoBiotics™ – Targeting and Harvesting the Microbiome

ActoBiotics™ platform is ideally suited to translate microbiome data

Selective reduction of microbiome subspecies which cause disease
Selective delivery of factors from microbiome subspecies which prevent disease



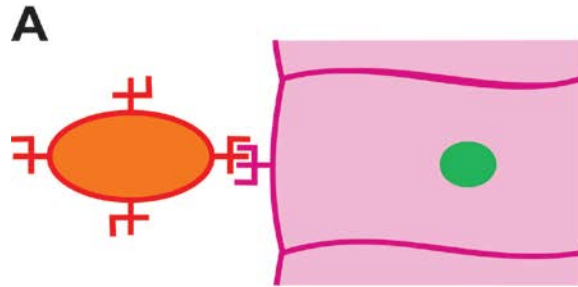
ActoBiotics™ - Targeted modulation of Microbiota

Cell Host & Microbe
Article

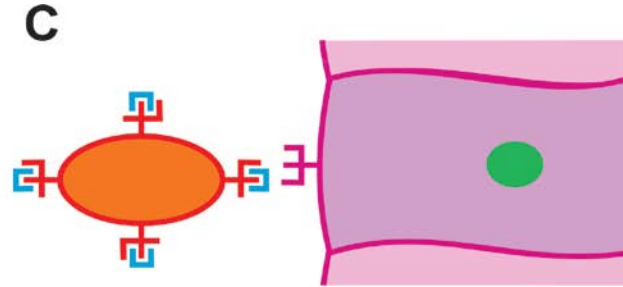


Fusobacterium nucleatum Promotes Colorectal Carcinogenesis by Modulating E-Cadherin/ β -Catenin Signaling via its FadA Adhesin

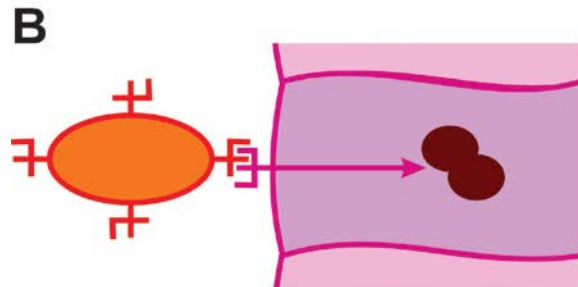
Mara Roxana Rubinstein,^{1,7} Xiaowei Wang,^{1,7} Wendy Liu,² Yujun Hao,^{3,6} Guilang Cai,⁶ and Yiping W. Han^{1,2,4,*}



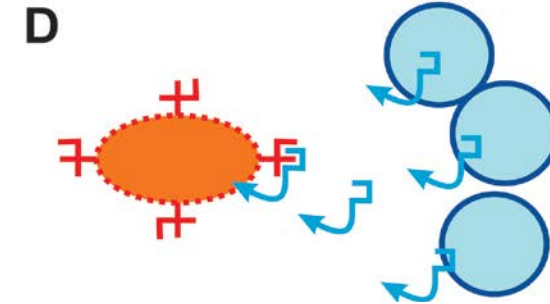
Healthy IEC: binding only



Mutant IEC; blocking E-peptide: no proliferation



Mutant IEC: onset of cell proliferation



L. lactis delivery of E-Peptide-toxin: Targeted bacterial lysis

ActoGeniX - Key Strengths

- Unique & versatile platform / diversified pipeline of products
- Local & targeted delivery: superior efficacy & safety
- Clinical validation: lead product Phase 2B-ready
- Fast development & low production costs
- Strong & broad patent estate & BLA exclusivity (12 years)
- Experienced Management team
- Validating business development deals

