



# The C1 Expression System Reinventing Biologic Vaccine & Drug Production



(OTCQX: DYAI)



## Safe harbor statement

Certain statements contained in this presentation are forward-looking statements. These forward-looking statements involve risks and uncertainties that could cause Dyadic's actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements. Except as required by law, Dyadic expressly disclaims any intent or obligation to update any forward-looking statements.



## The Company

- Dyadic (OTC: DYAI) is a publicly-traded global biotechnology company that engineers hyper-productive C1 fungal cells using its proprietary C1 expression system
- Market capitalization: \$62.6 million<sup>(1)</sup>
- Net cash: \$62.6 million<sup>(2)</sup>
  - No debt
- Leadership team with a successful track record

## The Technology

- The C1 platform is proven and has been applied in the industrials sector by multiple market leaders:
  - DuPont
  - BASF
  - Abengoa
  - Codexis/Shell
- Active biopharmaceutical partnerships with Sanofi Pasteur and ZAPI
- Excellent safety profile
- Dyadic retains exclusive sub-license rights to the C1 technology platform in biopharmaceutical indications

## The Opportunity

- Potential to remove a critical bottleneck in protein development and manufacturing processes
  - Allows for rapid scaling
  - High purity and production of biologics
  - Significantly lower CapEx and OpEx
- Potential to improve therapeutic vaccine & drug performance
- Dyadic is seeking partnerships to sub-license, or partner its C1 technology in the vaccine, antibody and biosimilar industries

(1) As of March 31, 2016. Share count represents 37.9 million common shares outstanding, includes 2.85 million shares repurchased through March 31, 2016.

(2) As of March 31, 2016. Reflects \$0 debt balance and excludes (i) ~\$7.4 million held in escrow from DuPont Transaction with expected release in July 2017, and (ii) \$2.1 million received 4/19/2016 from legal settlement.



## Mark Emalfarb

President and Chief Executive Officer

- President and Chief Executive Officer from 1979 to 2007, 2008 to present
- Founder of Dyadic and member of Dyadic's board of directors since 1979
- Chairman from 1979 to 2007, 2008 to 2015
- B.A. degree from the University of Iowa



## Michael Tarnok

Chairman of the Board

- Chairman of Dyadic since 2015
- Former Chairman of Keryx Biopharmaceuticals from 2009 to 2016
- Senior Vice President at Pfizer from 1989 to 2007
- M.B.A. from New York University



## Thomas Dubinski

Chief Financial Officer

- Vice President and Chief Financial Officer since 2014
- Management Consultant 2012 to 2014
- Finance Officer at Walgreens 2007 to 2011
- Director of Finance at Novartis 2005 to 2006
- Finance Director Abbott Laboratories 1984 to 2002
- B.S. in Accounting, University of Illinois, CPA Illinois



## Ronen Tchelet

VP of Research and Business Development

- Vice President of Research and Business Development since 2014
- Vice President at Codexis. Founder and Managing Director of Codexis Laboratories Hungary from 2008 to 2014
- Chief Technology Officer of API at Teva Pharmaceuticals from 2000 to 2007
- Ph.D. in Molecular Microbiology and Biotechnology from Tel Aviv University





C1 used by industry giants in areas such as ethanol and industrial enzyme production and vaccine development

SANOFI PASTEUR 

 POLFA TARCHOMIN<sup>®</sup>S.A.

 CODEXIS<sup>®</sup>

ABENGOA





ENMEX



 antibióticos



MARTEK   
life enriched.™

Acquired by  DSM  
BRIGHT SCIENCE. BRIGHTER LIVING.

  
IOGEN  
CORPORATION

 **BASF**  
The Chemical Company

Note: Refer to pages 37 and 38 for additional details on commercial applications of C1.



- The market acceptance and commercial use of the C1 technology in industrial biotechnology applications has been recognized by industry leading companies which culminated in DuPont's acquisition of Dyadic's Industrial Biotech business for \$75 million
- Sanofi Pasteur and the EU-funded ZAPI program are examples of industry and governmental funded research programs utilizing Dyadic's C1 technology in biopharmaceuticals
  - Sanofi R&D collaboration utilizes C1 expression system to speed up the development and production of new vaccines at a lower cost with potentially better immunogenicity
  - ZAPI program uses C1 to develop a platform suitable for the rapid development and production of vaccines and protocols to combat epidemic Zoonotic diseases
- There is a growing and critical need to bring affordable generic versions of biological vaccines and drugs to patients sooner and at lower costs
  - C1's unique growth and expression properties, coupled with its proven programmability, scalability high purity and yields, could be a game changer in developing and manufacturing biologic vaccines and drugs faster, in larger quantities with both less CapEx and OpEx, and potentially with even better performance
- Dyadic will leverage over two decades of experience in industrial biotechnology and technological advances in synthetic biology, genomics and biotechnology to pursue opportunities for using the C1 technology for biopharmaceutical applications
  - Vaccines
  - Biosimilars / biobetters
  - Novel biologic drugs



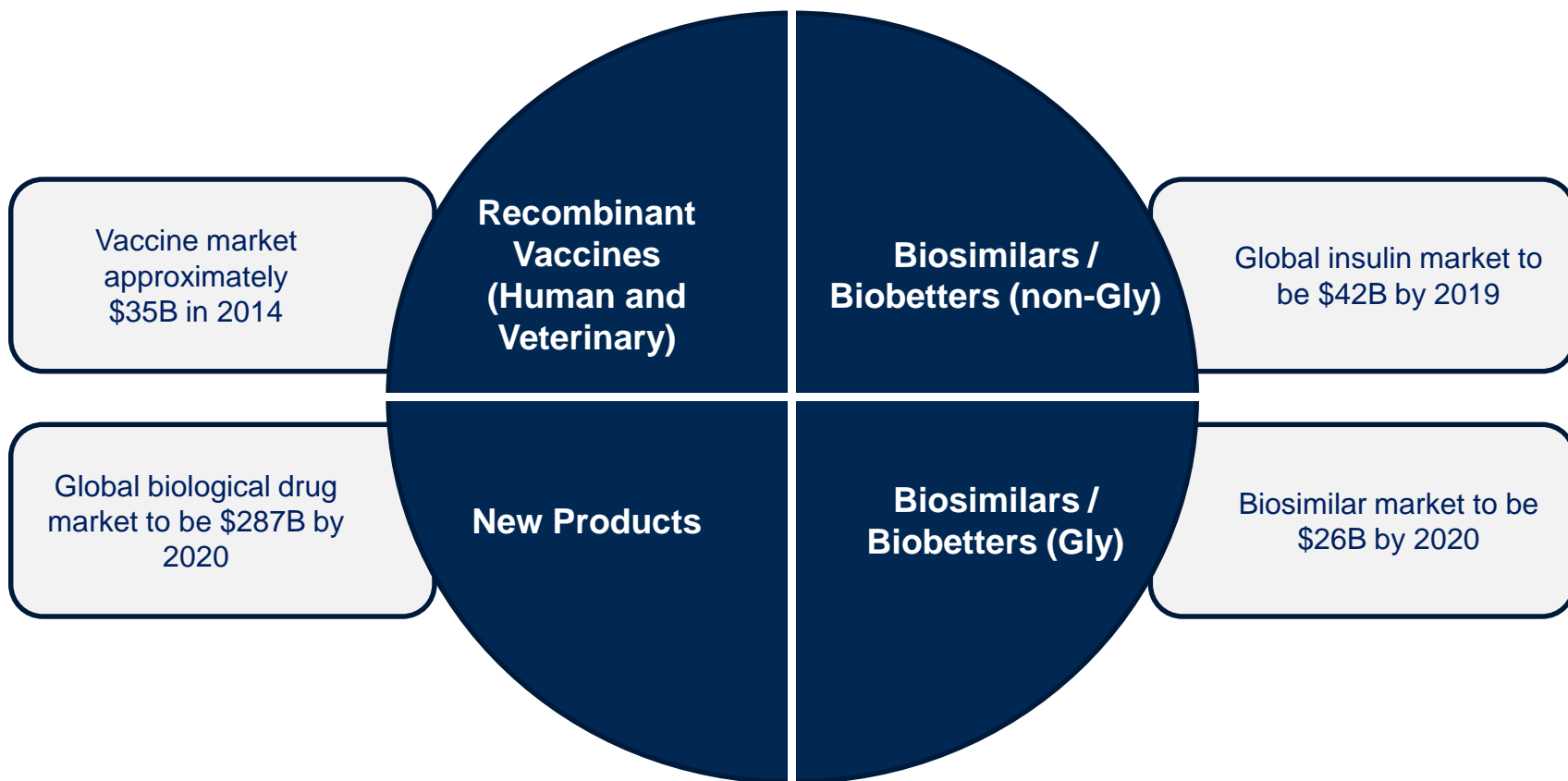
## **C1 For Biopharmaceuticals**

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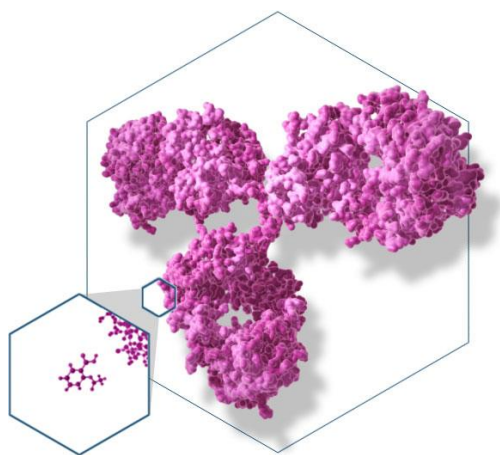
The C1 technology will be further developed to enable its use in the development and manufacturing of biologic vaccines and drugs







Due to their complexity, biologics can only be manufactured in living cells.



## THE C1 EXPRESSION SYSTEM



## **C1 is a robust and versatile fungal expression system that is designed to help address the critical bottlenecks of protein discovery, development, scale-up and commercialization**

- Developed in the early 1990's through two fortuitous UV-induced mutations which has been continuously improved through bioengineering
  - Novel cell morphology expresses high levels of purer proteins, under low viscosity in commercial manufacturing processes
- Serves as both a research and production host
- C1 genome annotated
- Advanced set of genetic capabilities and molecular tools
  - Allows for optimization of the host production organism
  - Enables rapid and efficient cloning of heterologous genes
  - Including ability to readily knock out proteases
- Potentially develop new products with less time, cost, and improved performance
- Broad platform capabilities validated through 17 years of R&D and 15 years of product sales and partnerships
- Successfully manufactured a variety of commercial products at industrial scale in 5 countries over 17 years



## Technology

- Mature system for production of heterologous proteins
- Excellent safety profile
- Fully programmable, patented technology

## Production

- Low cost, commercially scalable fermentation at up to 500,000 liter scale
- High purity and yield, 100+ grams per liter
- No animal-derived ingredients used
- Short development and fermentation times

## Product Attributes

- Potential to generate improved immune response in vaccines
- Favorable glycoprofile can be modified to become 'human neutral' to lessen immunogenicity



## ***Generally Recognized as Safe (GRAS) status acknowledged by the FDA***

- ❖ C1-cellulase accepted by FDA on September 29, 2009
- ❖ GRAS Notification letter is a public statement by FDA acknowledging Dyadic's safety determination for the intended uses of C1
- ❖ GRAS Notification letters are broadly recognized in the food and consumer products industries as the safety standard



## **C1 strain non-toxic**

- ❖ Pathogenicity and toxigenicity data: strain is non-infectious and no known toxins are produced
- ❖ Peer-reviewed scientific literature have confirmed — no known pathogenicity
- ❖ No mycotoxins found

## **C1 enzyme testing**

- ❖ In vivo feeding trails:
  - 14 day dose study in rats
  - 13 week subchronic rat study
- ❖ Genotoxicity testing:
  - AMES bacterial mutagenesis
  - Chromosomal aberration test
  - Genetic mutation test
- ❖ **No adverse effects observed**
- ❖ **No foreign DNA**
- ❖ **Safety confirmed**



## Wild type

### 1992

- Discovered C1 wild type strain which naturally produced neutral cellulase enzymes

## 1<sup>st</sup> breakthrough

### 1995-96

- Mutation led to development of high cellulase C1 strain with unique morphology
- Commercial launch of C1 enzymes for textile industry

## Genomic annotation, 2<sup>nd</sup> breakthrough

### 2005-2015

- Sequenced and annotated the C1 genome
- Developed low cellulase C1 strain, enabling the commercial production of "purer enzymes"
- Hyper productivity reached 100 g/l with ~ 80% purity

## Future development

### 2016 - 2018

- Develop robust high C1 expression host strain for Biopharmaceutical applications
- Develop versatile easy to use construct library based on system biology
- Develop Glyco-engineered C1 strain to resemble human protein-glycosylation structure

1979

1992

1995

2000

2005

2015

2016

2018

## Dyadic Founded

### 1979

- Dyadic Founded

## Development of a world-class protein production technology

### 1997-2007

- Developed molecular toolkit for optimizing C1-based recombinant protein production for commercialization
- Produced variety of commercial products using the C1 strains
- Successfully expressed human therapeutic proteins in C1
- High throughput robotic screening developed and patented

## C1 for Bio- industrial Enzymes

### 2009 - 2015

- Developed comprehensive enzyme library
- Produced first commercial product using LC C1
- GRAS status acknowledged by FDA
- Developed HC strains for biofuel enzyme production
- Hyper productivity reached 100 g/l with ~ 80% purity

## C1 for Biopharmaceutical applications

### 2016 -

- Develop C1 platform as an expression host for:
  - Vaccines
  - Biosimilars
  - New products



## Dyadic has a history of strong scientific collaborations

### Enzyme Development

- Isolation, discovery and characterization of the enzymes expressed by the wild type and mutants of the C1 fungus

### Genome Annotation

- Performed annotation of the C1 genome, allowing identification of key metabolic functions that influence expression and glycosylation

### C1 Strain Development, Optimization

- Development programs for gene expression, gene knock outs and gene discovery (low protease C1 strains and C1 molecular toolkit)

### Fermentation, Process Development, Optimization

- Development, scale up and commercial scale production of enzymes and other proteins utilizing the C1 platform technology



Moscow State  
University



Kluyver CENTRE





## C1 Attributes

- Novel cell morphology expresses high levels of purer proteins, under low viscosity
- Advanced set of genetic capabilities and tools
  - Including ability to readily knock out proteases
- C1 genome annotated
  - Allows identification of functions that influence gene expression and facilitates use of advanced genetic technologies
- Commercially proven at up to 500,000 liter scale

## Advance C1 Technology

- Using advanced molecular tools to modify C1's genetics to address the expression needs of the biopharmaceutical industry
  - Further engineer C1 cells to optimize biopharmaceutical protein stability and yield
  - Glycoengineer C1 cells to express human like non immunogenic glycosylated antibodies
  - Optimize the fermentation and downstream purification processes for the production of biopharmaceuticals

## Progress with commercial partners

- Sanofi reported C1 produced antigen generated an equal, or better, immune response in mice than the industry standard antigen.
- On schedule with cloning and expression of different antigens of interest to the ZAPI Consortium
- Generated interest with multiple pharmaceutical and biotech companies about potential research and other collaboration opportunities

## Freedom to Operate

- No royalty stacking<sup>(1)</sup>

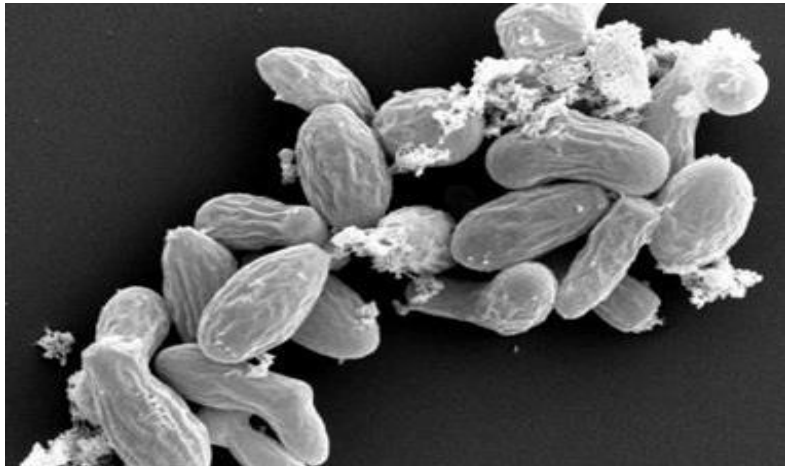
(1) If DuPont makes an improvement, and we choose to utilize it, there will be a royalty due DuPont, and vice a versa. DuPont will owe Dyadic a royalty upon commercialization





## Two serendipitous mutations led to the creation of the world class C1 expression system

- Synthetic biology start-ups – large and small – struggle with the reality of scaling up microscopic cellular factories into profitable business models
- Dyadic's patented and proprietary C1 expression system is being used to produce biological products at very high yields, low cost and in large commercial fermenters



**High yields, high purity, low cost  
at industry leading scale**

**100 g/L**

- Over 100 grams per liter protein

**80%  
purity**

- Up to 80% of target protein has been achieved

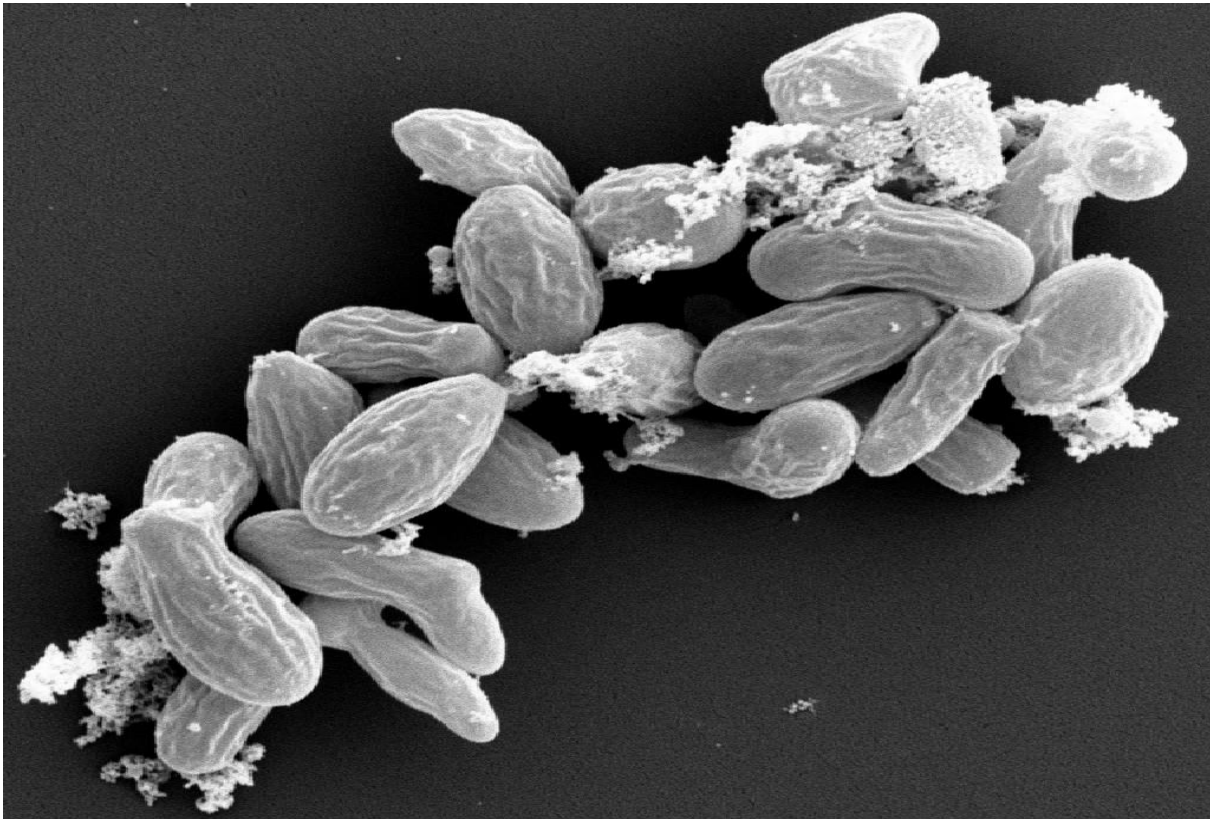
**500,000  
liter scale**

- Currently produced in up to 500,000 liter scale

# C1 unique morphology



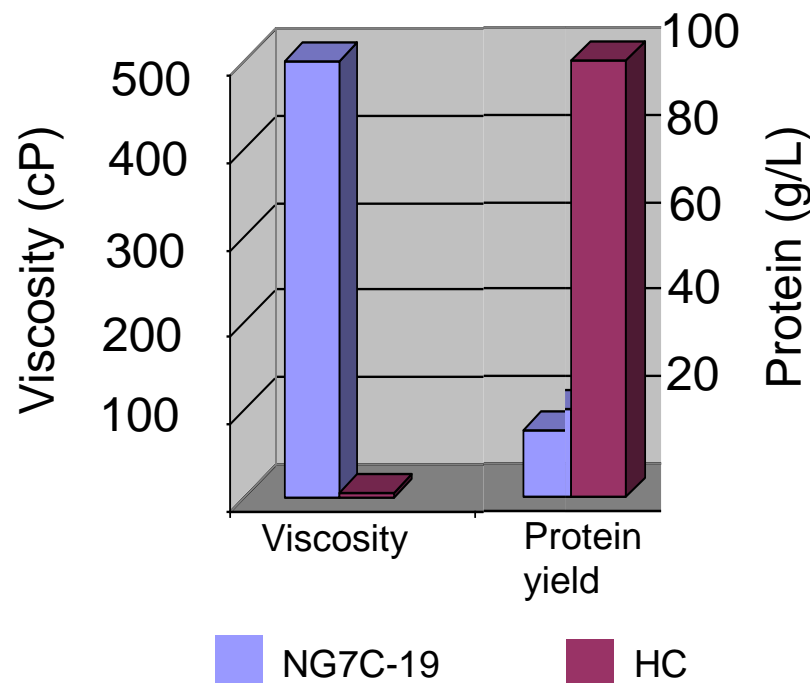
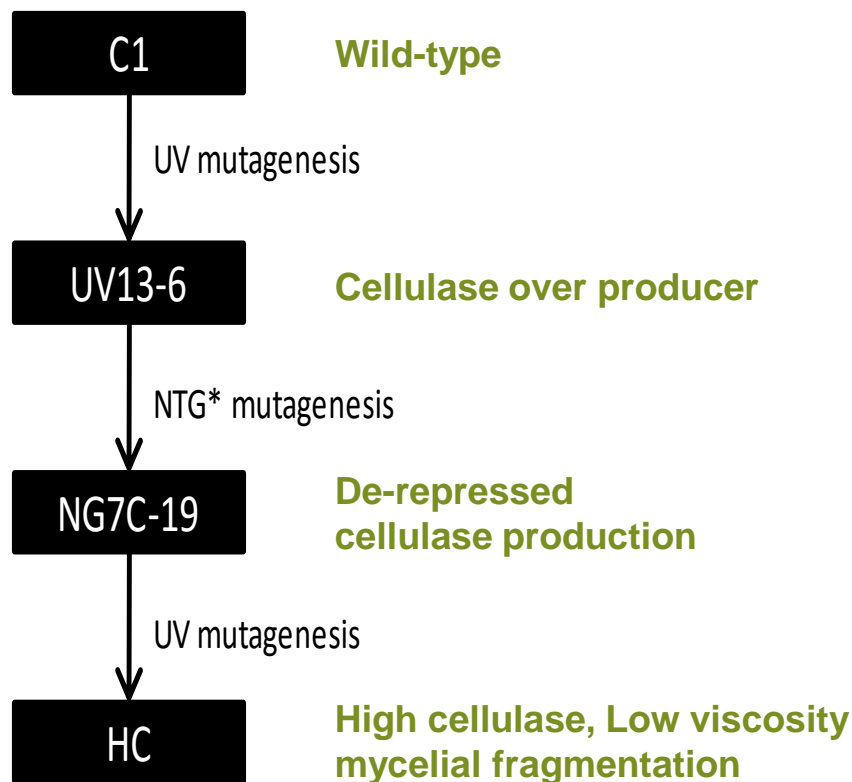
**Morphology change: hyper productivity, low viscosity**



C1-propagules by scanning microscopy. Propagules instead of hyphae: low viscosity, high productivity.

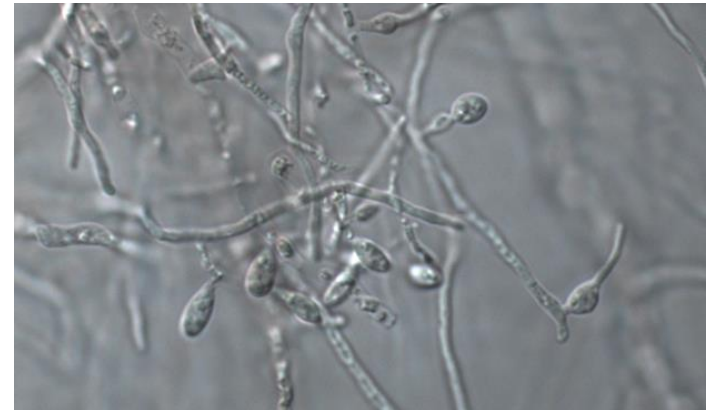
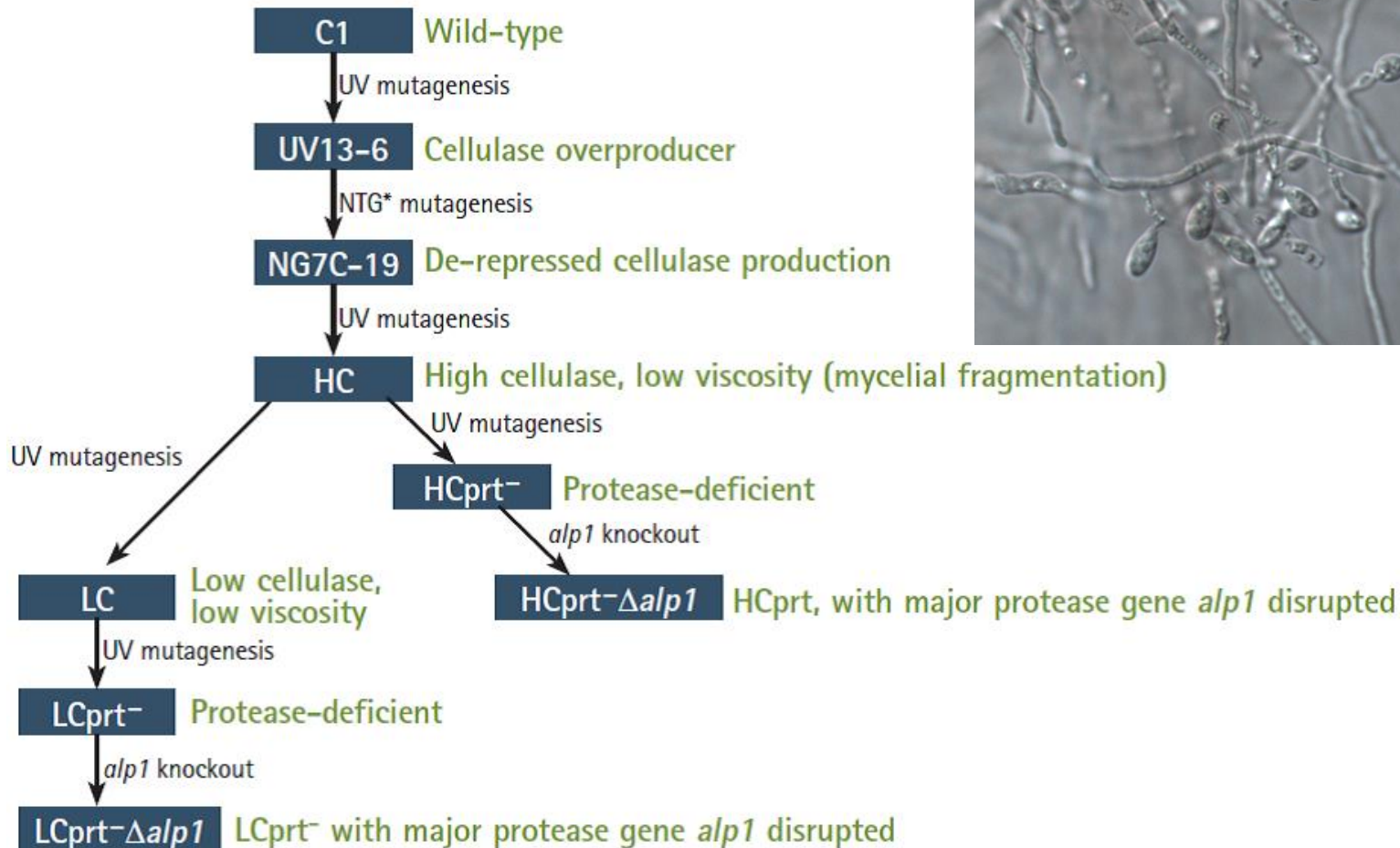


## Development lineage of protein hyper-producing strains



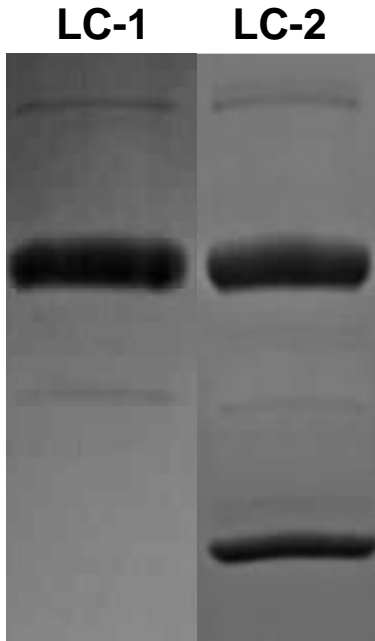


## Development high productivity low protease activity of host strains for specific proteins productions



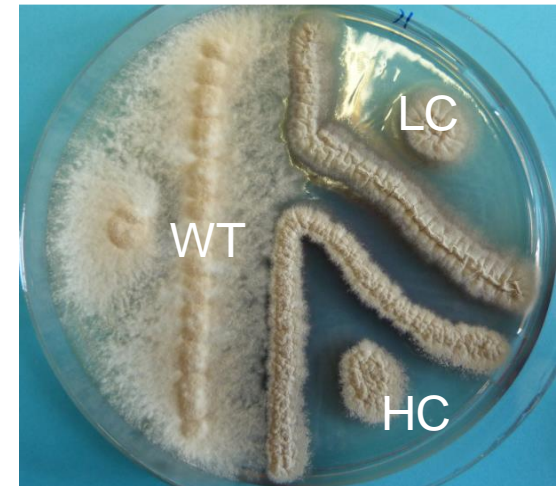


## LC expression of specific proteins



- Dyadic's C1, LC strains successfully used in production of single and multiple proteins derived from fungal, bacteria, bacterial-directed evolution, mammalian, human and viral strains
- The expression reaches high production levels of secreted proteins – > 100 g/l with ~ 80% purity of the targeted protein
- The LC strain/s is fermented at large commercial scale

## C1 strain types



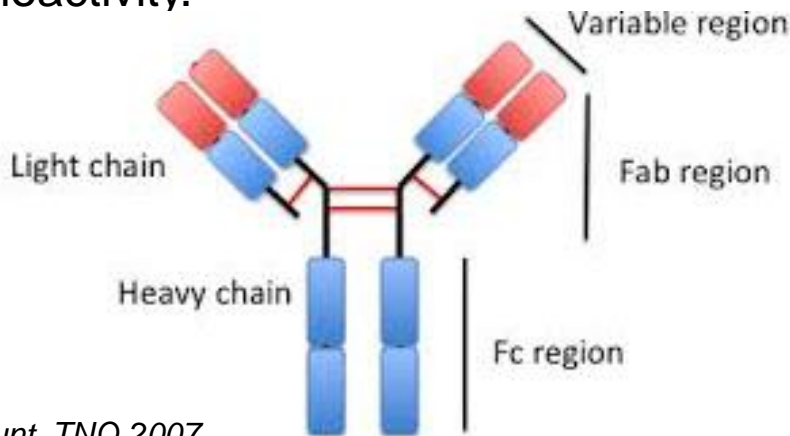
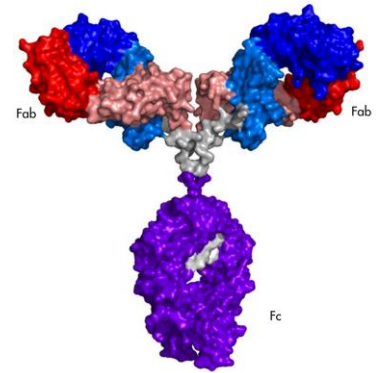
C1 LC “White Strains” have very different morphology than the C1 Wild Type Strains





## Produced biologically active monoclonal antibodies in C1

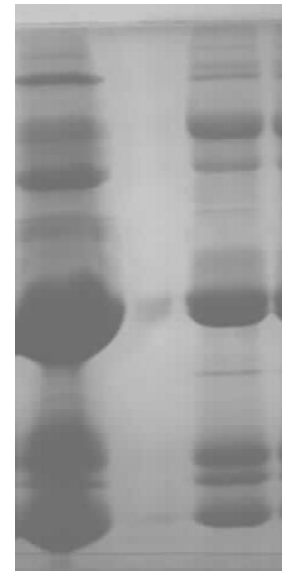
- Expression was achieved of both: heavy and light chains were obtained.
- Heterodimeric antibody molecules were formed efficiently, allowing simple purification of the protein from the culture fluid using Protein A.
- Cell-based bio-assays performed revealed almost complete bioactivity.



Peter Punt, TNO 2007

Heavy chain

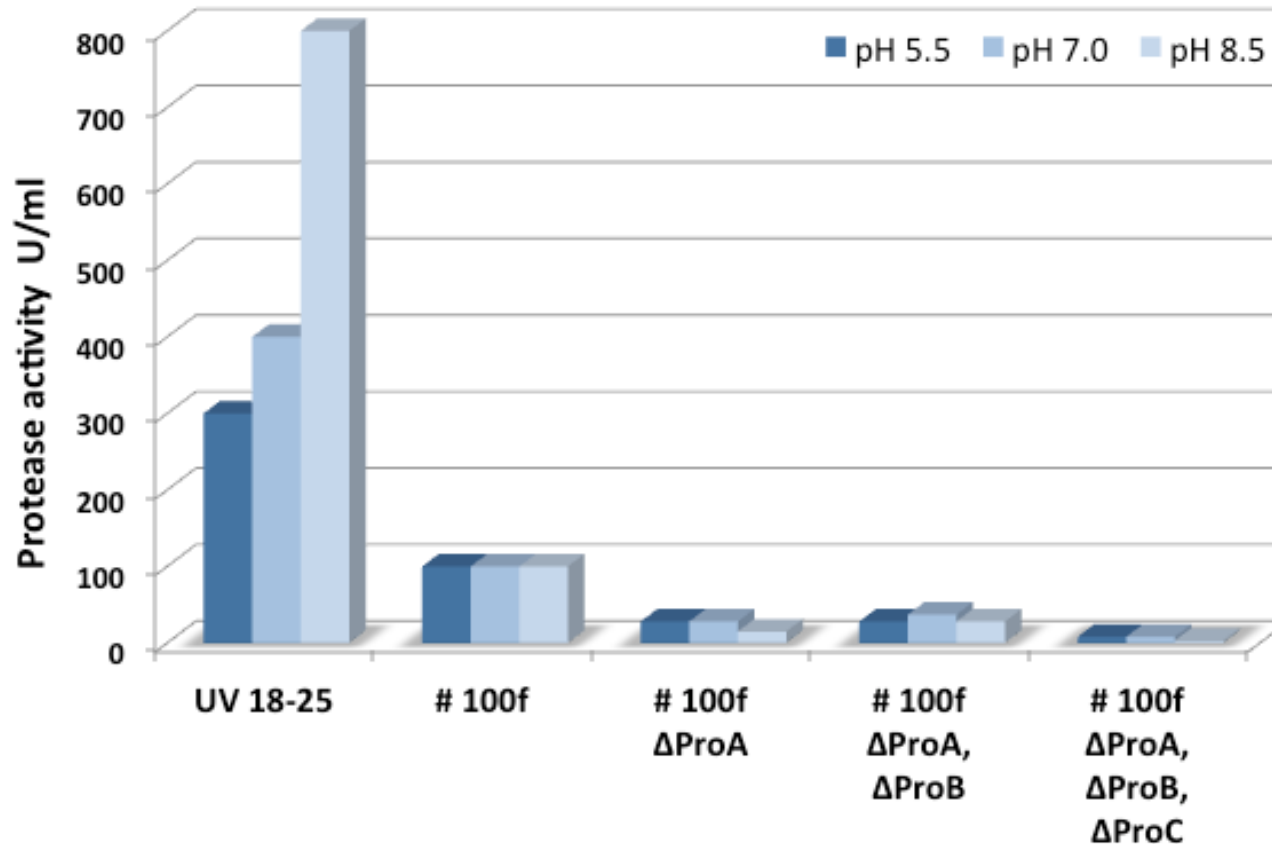
Light chain





## Host strains with low protease activity developed for heterologous protein production

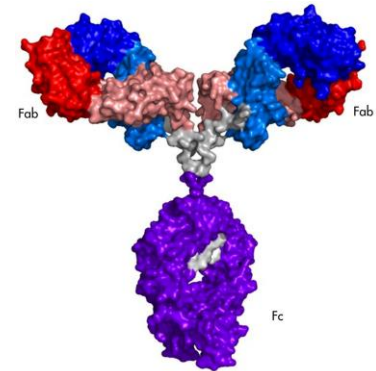
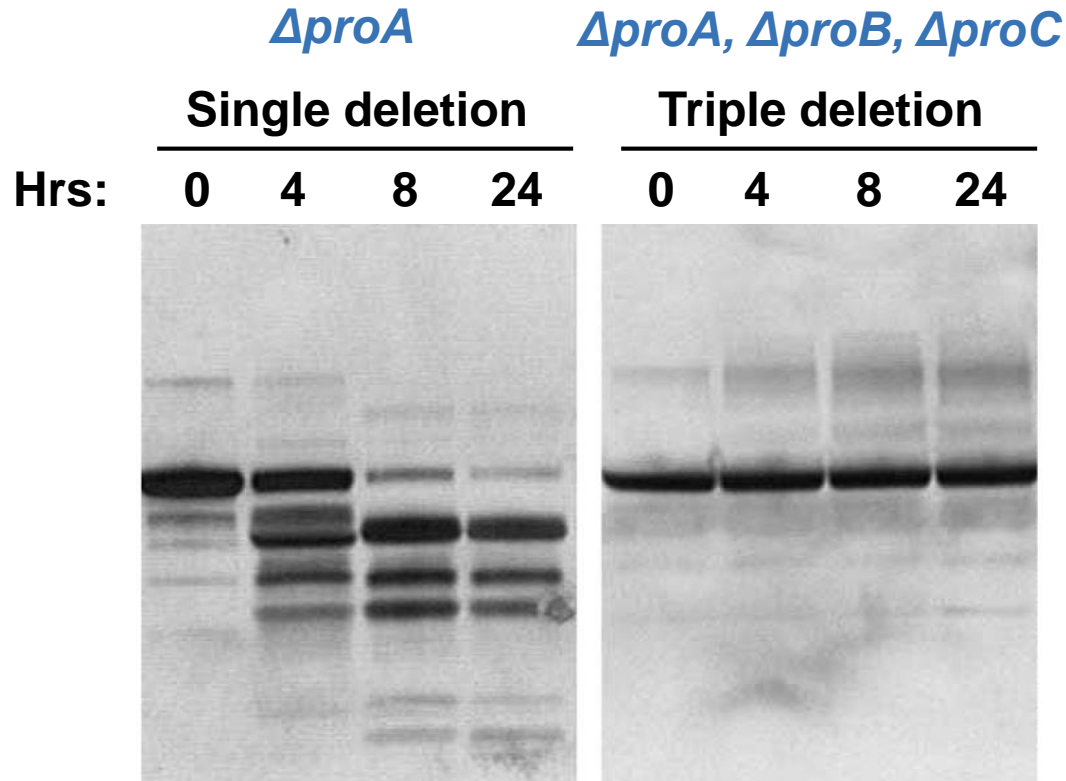
### Protease Activity







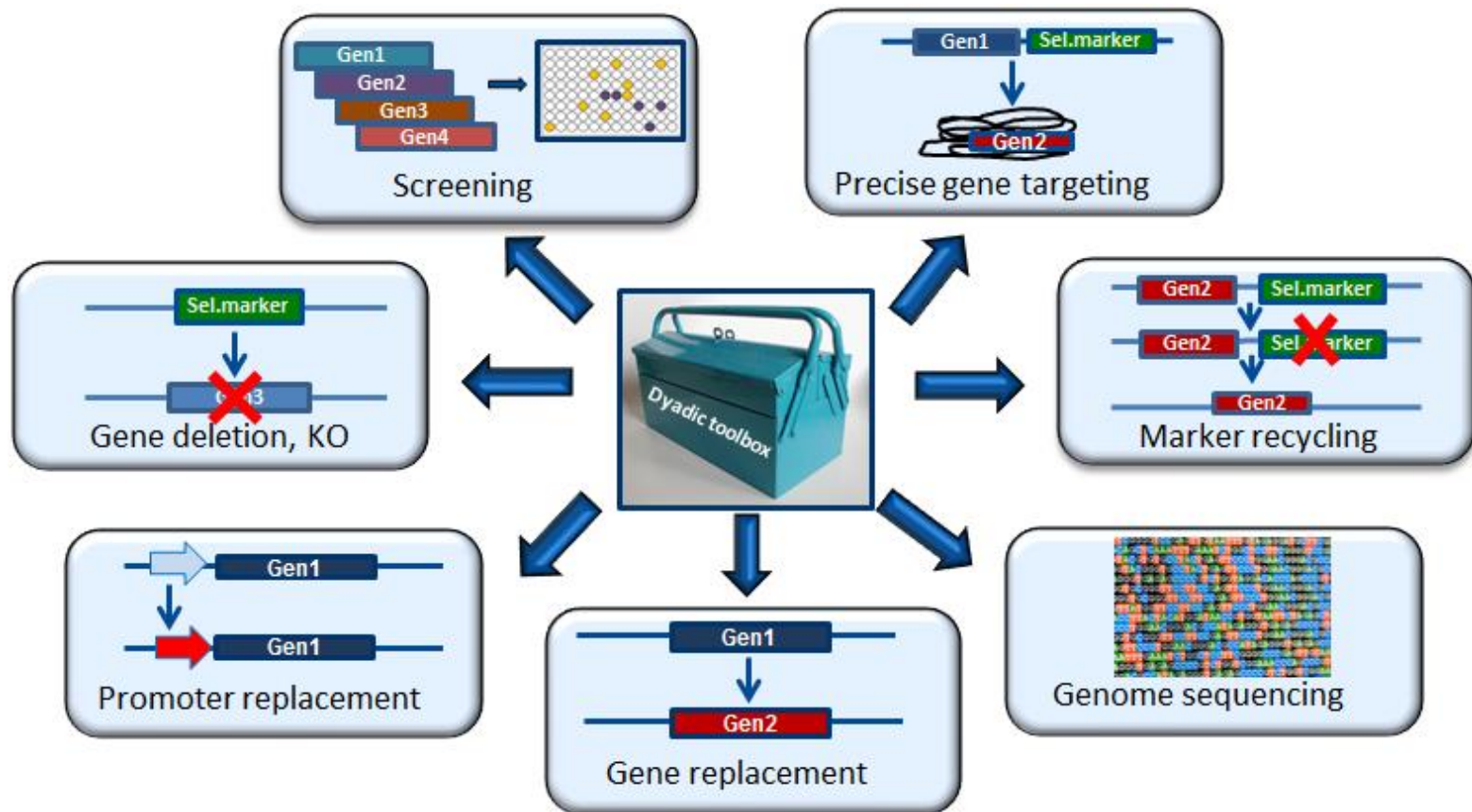
## *In Vitro* stability of heavy chain against C1 fermentation culture filtrates



Light chain: **no degradation**

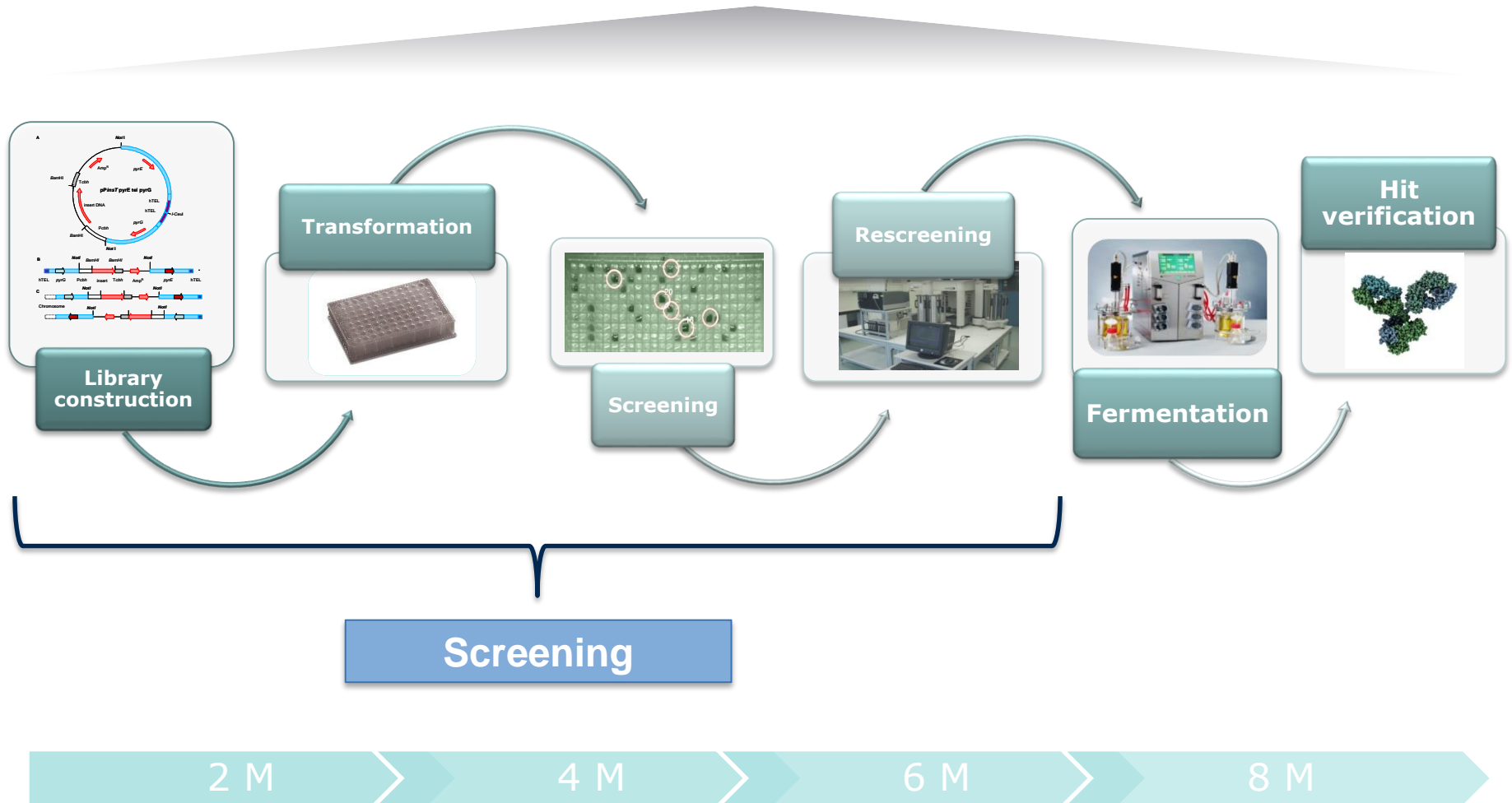


## Dyadic's advanced genetic toolkit for manipulation of C1

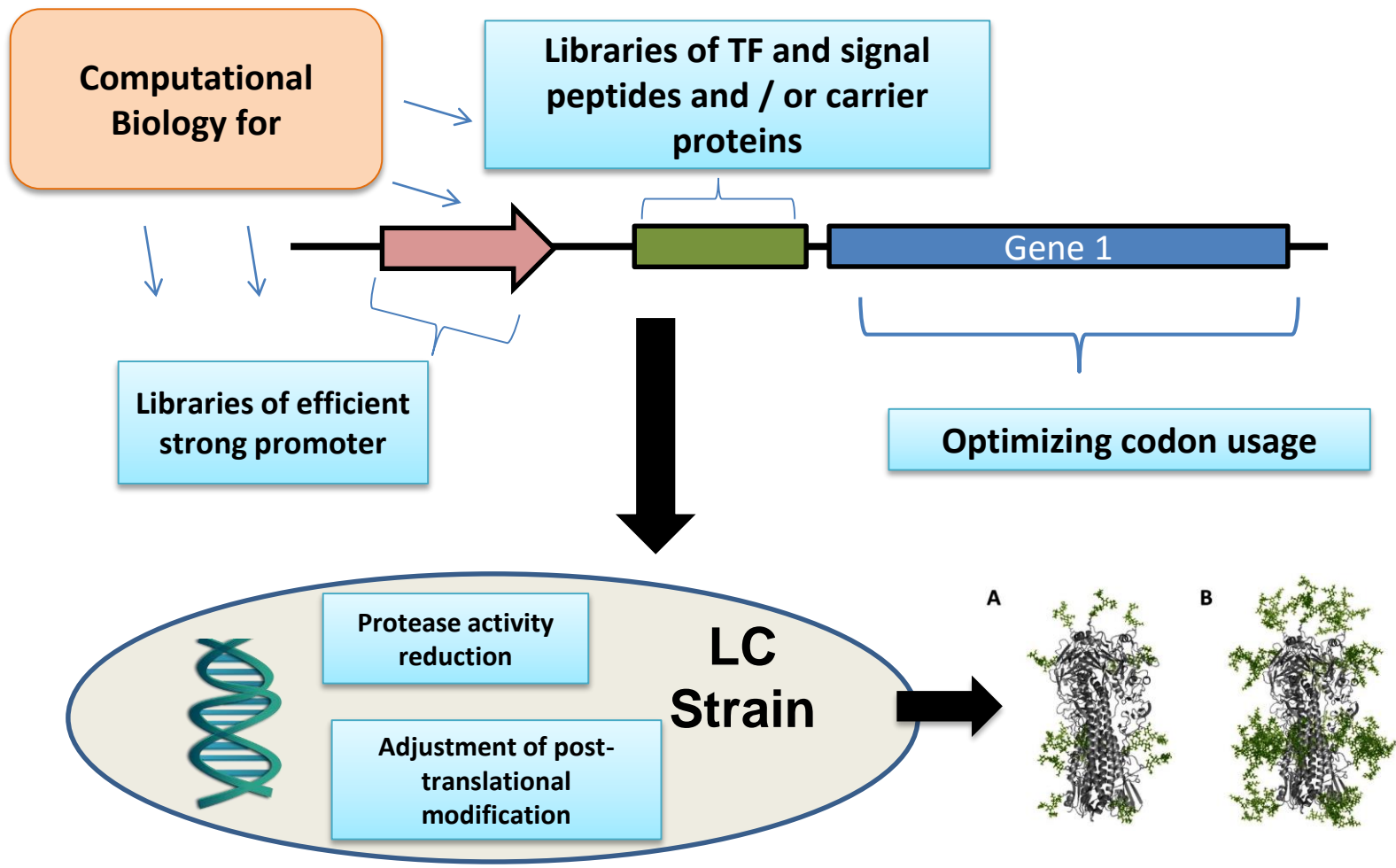




# MTP-based C1 fermentation property enables rapid screening of any new inserted protein



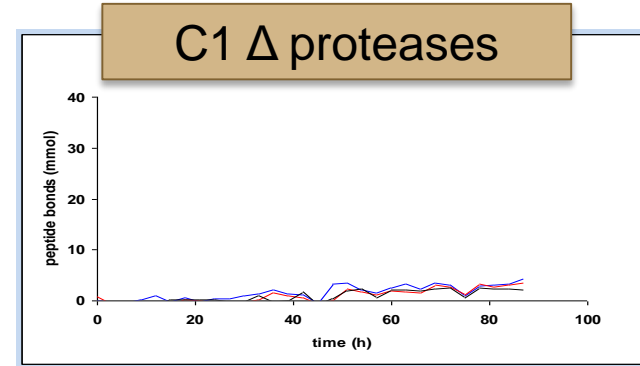
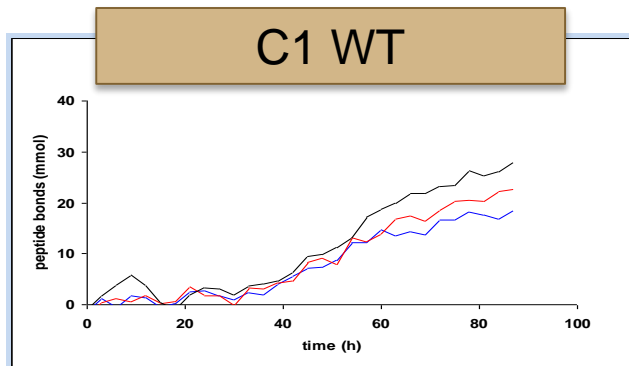
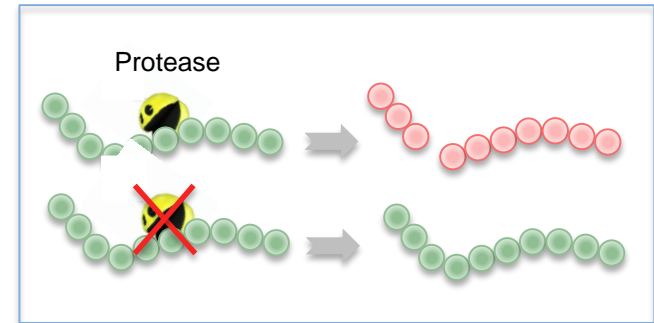
Advanced genetic manipulation methodologies enable rapid and efficient cloning of heterologous genes





## Protease deficient C1 host strains

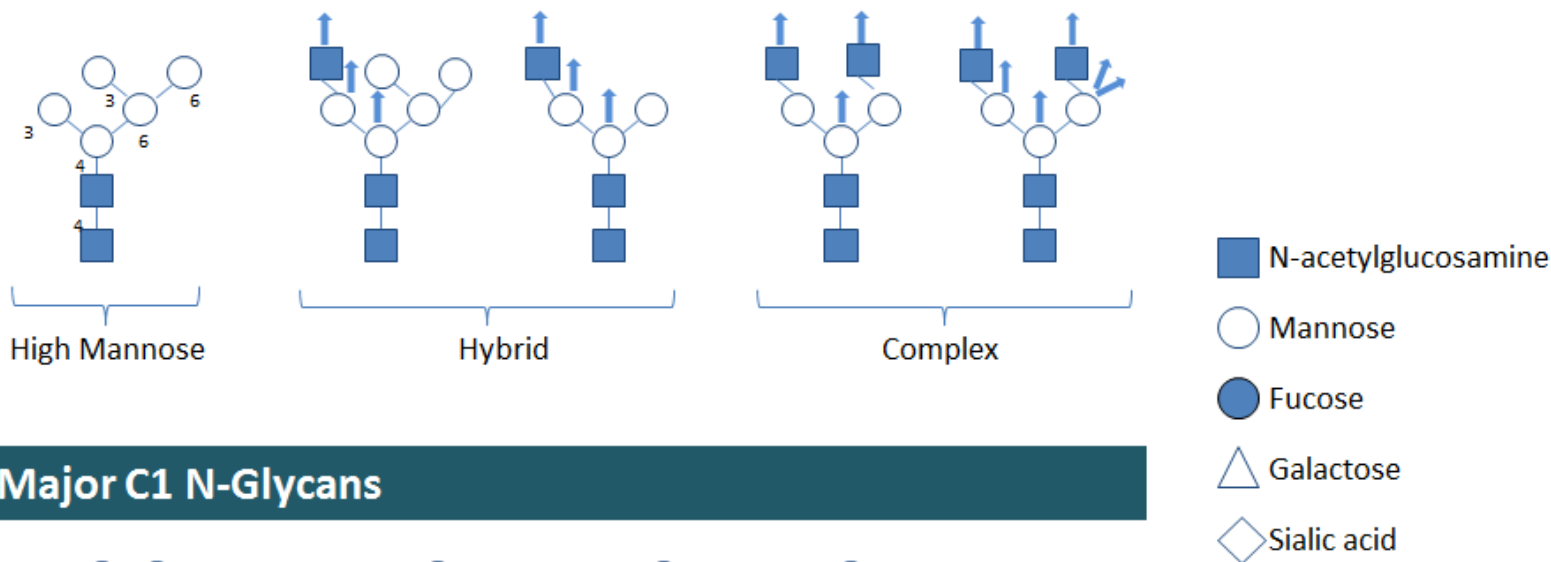
- ❖ Protease deficient strains were developed to improve the stability of expressed heterologous proteins.
- ❖ Elimination of 3 specific active proteases resulted in complete stable light and heavy chain of IgG1 expressed in C1.
- ❖ State of the art molecular engineering methods based on computational biology will enable us to eliminate specific proteases to stabilize biologic proteins.



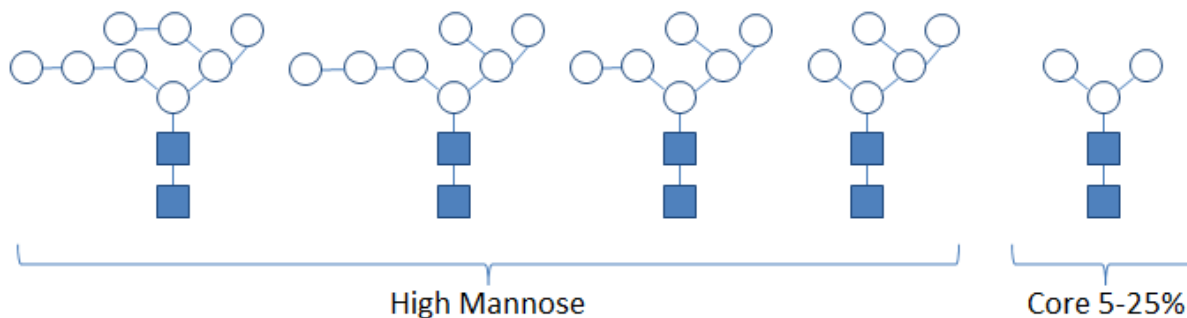


## C1 Glycans resemble human structure

### Major Vertebrate N-Glycans

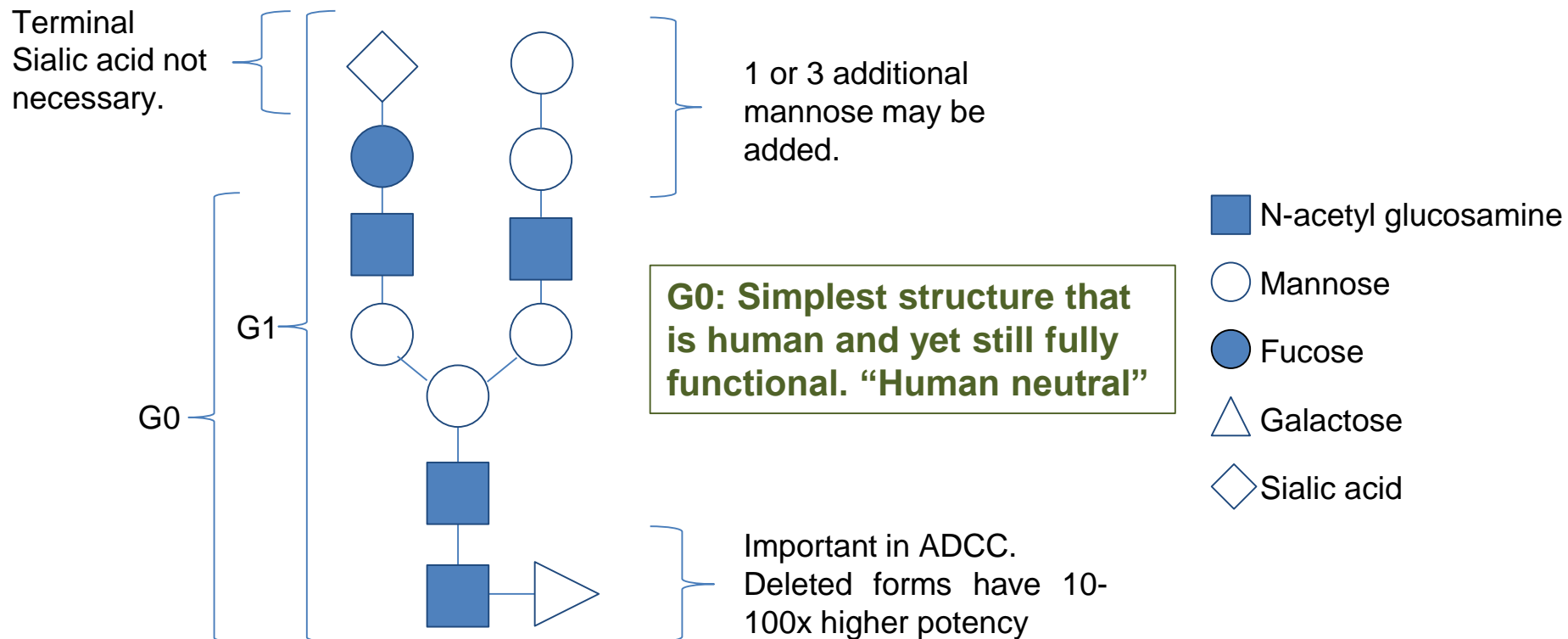


### Major C1 N-Glycans





## C1 Glycoengineering for biosimilars and biobetters applications



***Dyadic will very soon collaborate with Biotechnology group to use state of the art technology for glyco-engineering C1 to resemble human structure.***





## Vaccine Applications

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- The vaccine market quadrupled in value from \$5B in 2000 to almost \$24B in 2013
  - Influenza vaccine market: estimated to grow from \$2.9B in 2011 to \$3.8B by 2018
    - Need for better patient immunization in addition to lower cost
  - US: \$1.6B in 2011 to \$2.2B in 2018
- Global market projected to rise to \$100B by 2025
- There are more than 120 new products in the development pipeline
- 60 products are of importance for developing countries
  - Vaccines are becoming an engine for both the human and animal pharmaceutical industry
  - Changing status of vaccines within the pharmaceutical industry





## R&D collaboration to utilize C1 expression system for vaccine applications

- Sanofi Pasteur is one of the largest vaccine companies in the world
- Goal is to speed up the development & production of new vaccines at a lower cost
- Initial C1 produced vaccine showed an equal or better immune response in mice trials than the existing vaccine
  - Dyadic needs to deliver sufficient quantities of additional vaccines produced using C1 for Sanofi to test in mice trials
  - Objective of the additional mice trials is to see if the same encouraging results that were obtained in the first mice trial reported in a press release on October, 7 2015, will be reproduced with the additional C1 produced vaccines
- We are working on expressing and producing sufficient quantities of additional vaccine variants in the Sanofi research project for further evaluation by Sanofi
- Expect a go / no go decision from Sanofi at end of 2016 or early 2017





- Program sponsored by the EU to develop a platform suitable for the rapid development and production of vaccines and protocols to fast-track registration of developed products to combat epidemic Zoonotic diseases that have the potential to effect the human population

## Select Commercial Parties

## Select Academic Institutions



**Utrecht University**



**Universiteit  
Leiden**



- Dyadic Nederland's, BV. is using C1 to express vaccines and neutralizing agents which if such research is successful we anticipate the C1 platform may be chosen as a preferred platform within the ZAPI research project
  - Two of the objectives we hope to attain through the ZAPI funded research project are as follows:
    - Additional examples of vaccines and neutralizing reagents against emerging pathogens expressed from C1
    - C1 produced proteins regulatory pathway identified, and carried out at least in part, through collaborative partnerships between human and veterinary medical institutions, governmental regulatory agencies, expert academic groups and industrial partners
- ZAPI is a multi year project which full results may not be known for 3 - 4 years

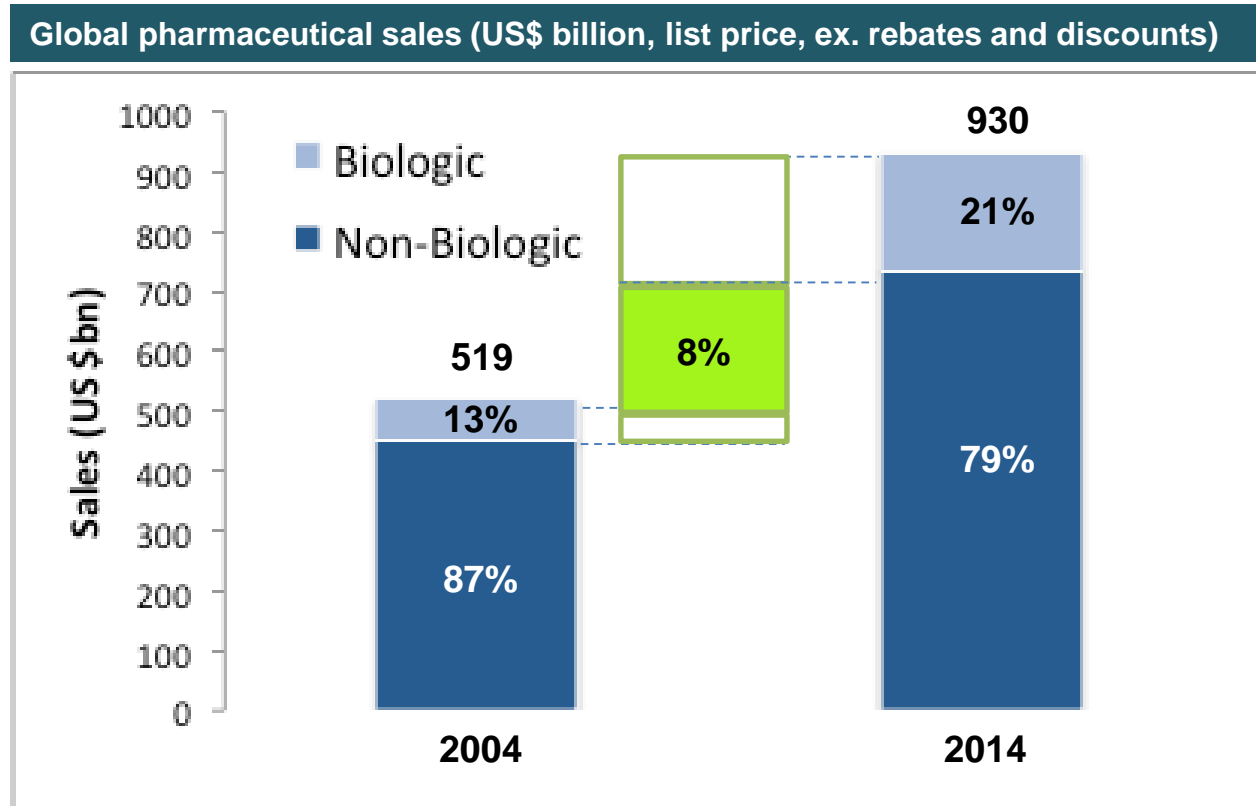


## **Biologics Applications**

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**Biologics are the fastest growing drug segment**



**Biologics currently account for 21% of total global spending on medicines and are expected to grow at 10.1% CAGR until 2020 to \$287B**



## C1 Attributes

- Novel cell morphology expresses high levels of purer proteins, under low viscosity
- Advanced set of genetic capabilities and tools
  - Including ability to readily knock out proteases
- C1 genome annotated
  - Allows identification of functions that influence gene expression and facilitates use of advanced genetic technologies
- Commercially proven at up to 500,000 liter scale

## Advance C1 Technology

- Using advanced molecular tools to modify C1's genetics to address the expression needs of the biopharmaceutical industry
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## Progress with commercial partners

- Sanofi reported C1 produced antigen generated an equal, or better, immune response in mice than the industry standard antigen.
- On schedule with cloning and expression of different antigens of interest to the ZAPI Consortium
- Generated interest with multiple pharmaceutical and biotech companies about potential research and other collaboration opportunities

## Improving capabilities

- Added two new Board members with pharmaceutical industry experience
- DuPont Agreement provides us with flexibility, access, and expertise for advancing C1 technology
- Expecting to add additional business development & licensing resources
- Strong balance sheet





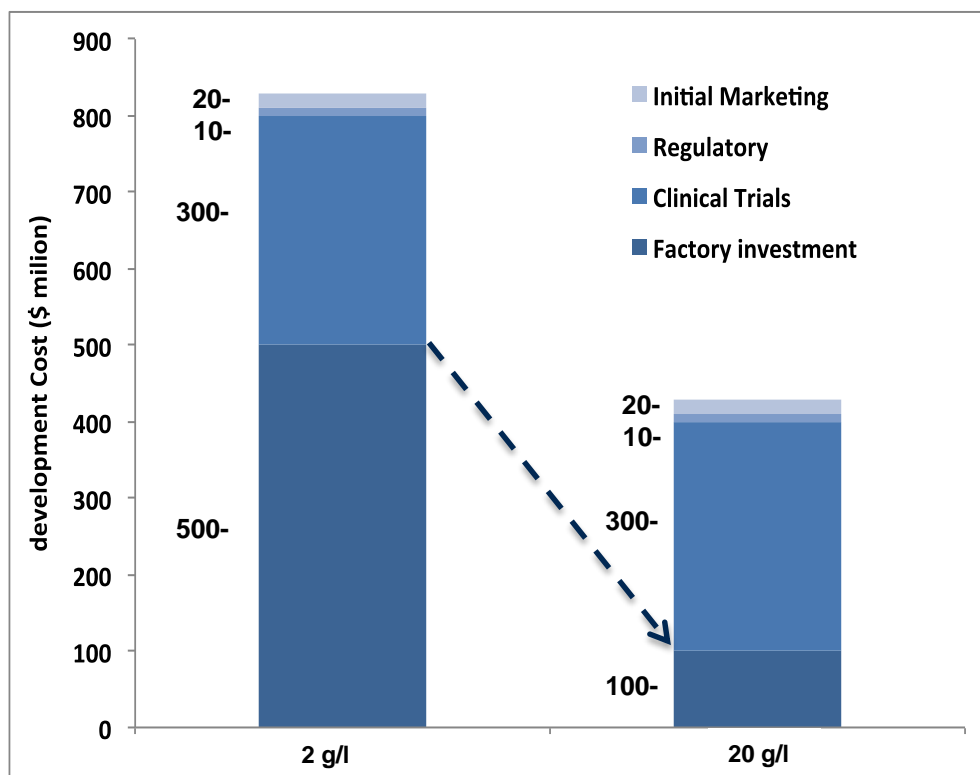
## Therapeutic Biologic Drug Market to Soar at 10.1% CAGR till 2020, ~ \$287 Billion

- C1 is a developed host system that has high potential to be used for the biopharmaceutical market
- For vaccine production C1 system may offer rapid development time and flexible production capacity at different sites
- The global biosimilar market is growing steadily since the need for lower cost biologics among the developed and pharma emerging countries is critical
  - \$1.9B market in 2014 is expected to reach \$25.5B by 2020, growing at an impressive CAGR of 54.4%
- The increasing biosimilar competition will eventually drive the cost down to 45% and below
- C1 high productivity system, for Vaccines, mAbs and other biologics, will offer significant saving in CapEx and operational cost



## C1's high productivity lowers plant construction & drug production costs

### C1 advantage in saving CapEx investment



■ When a 10,000 liter production fermenter can be reduced to a 200 liter production the savings are significant in 3 ways:

- Capital investment required to build launch capacity
- Factory with launch capacity needs to be constructed 24 month before FDA approval, or very costly CMO
- FDA license easier for small factory

WE CANNOT SOLVE OUR PROBLEMS  
WITH THE SAME THINKING  
WE USED WHEN WE  
CREATED THEM

- Albert Einstein

