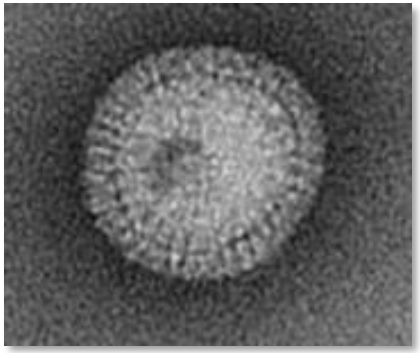
MultiBac IC-BEVS for Producing VLP-based Vaccines

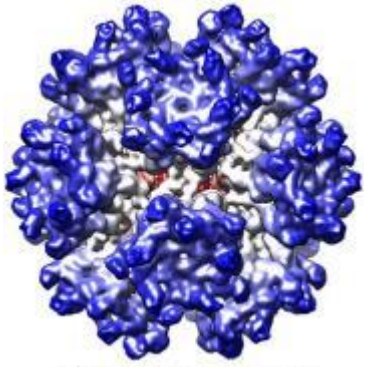
DCVMN 19th Annual Meeting Kunming 2018

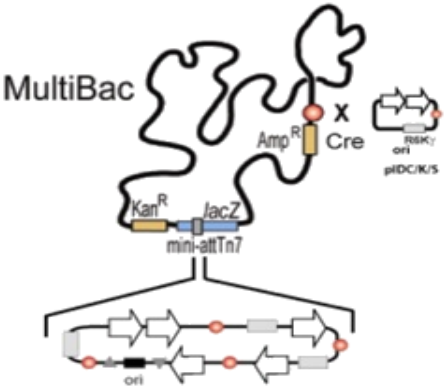


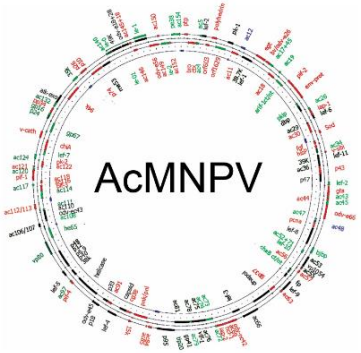
Imre Berger

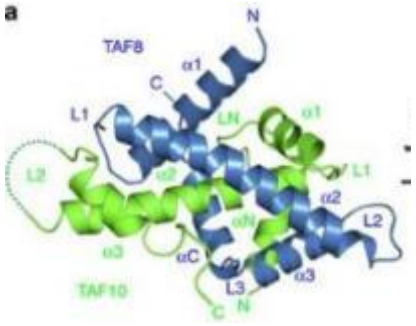
University of Bristol

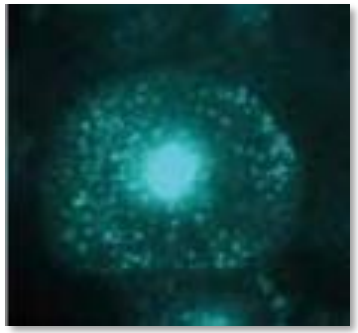
BrisSynBio Centre



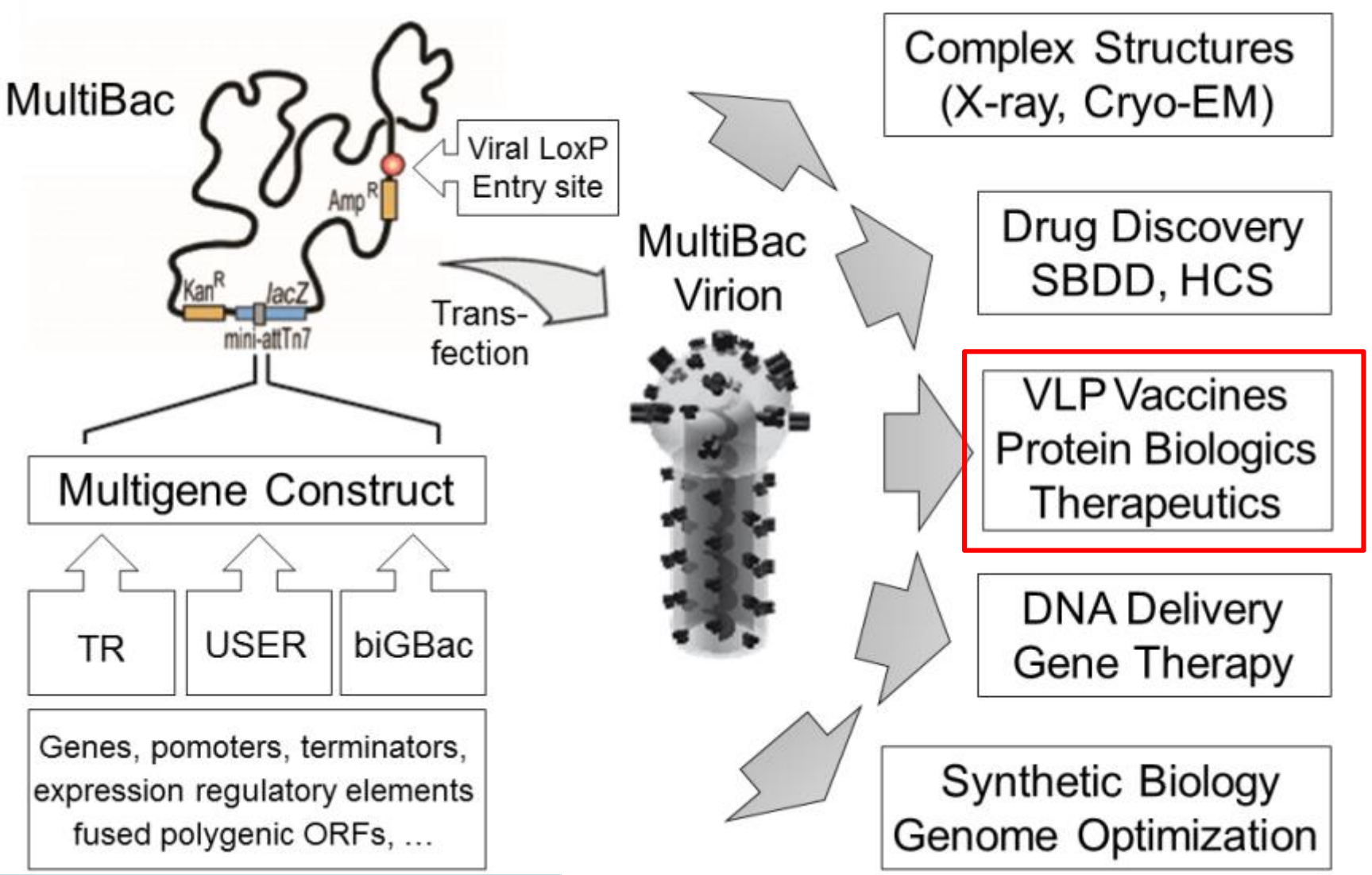








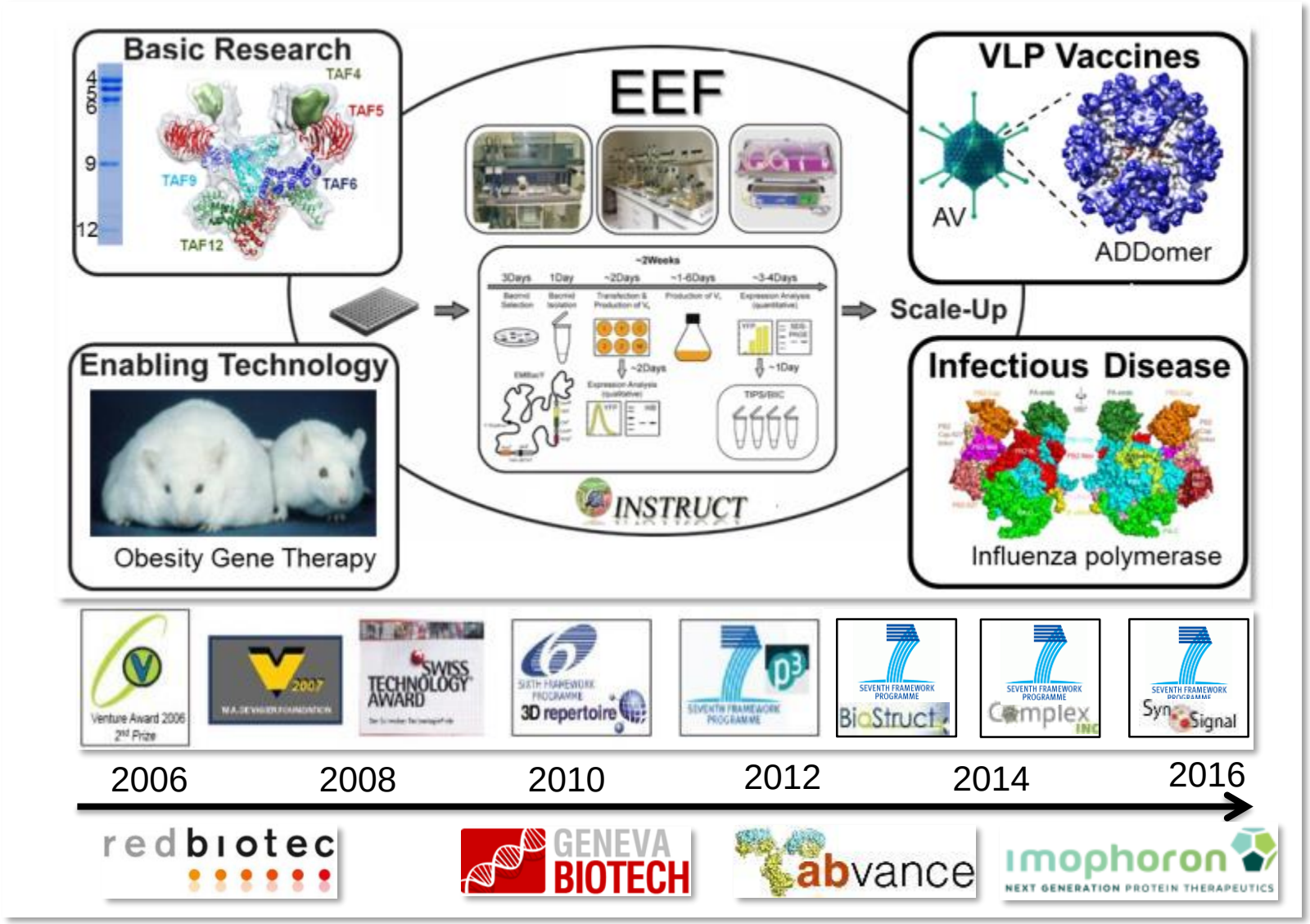
MultiBac – Complex Production Technology



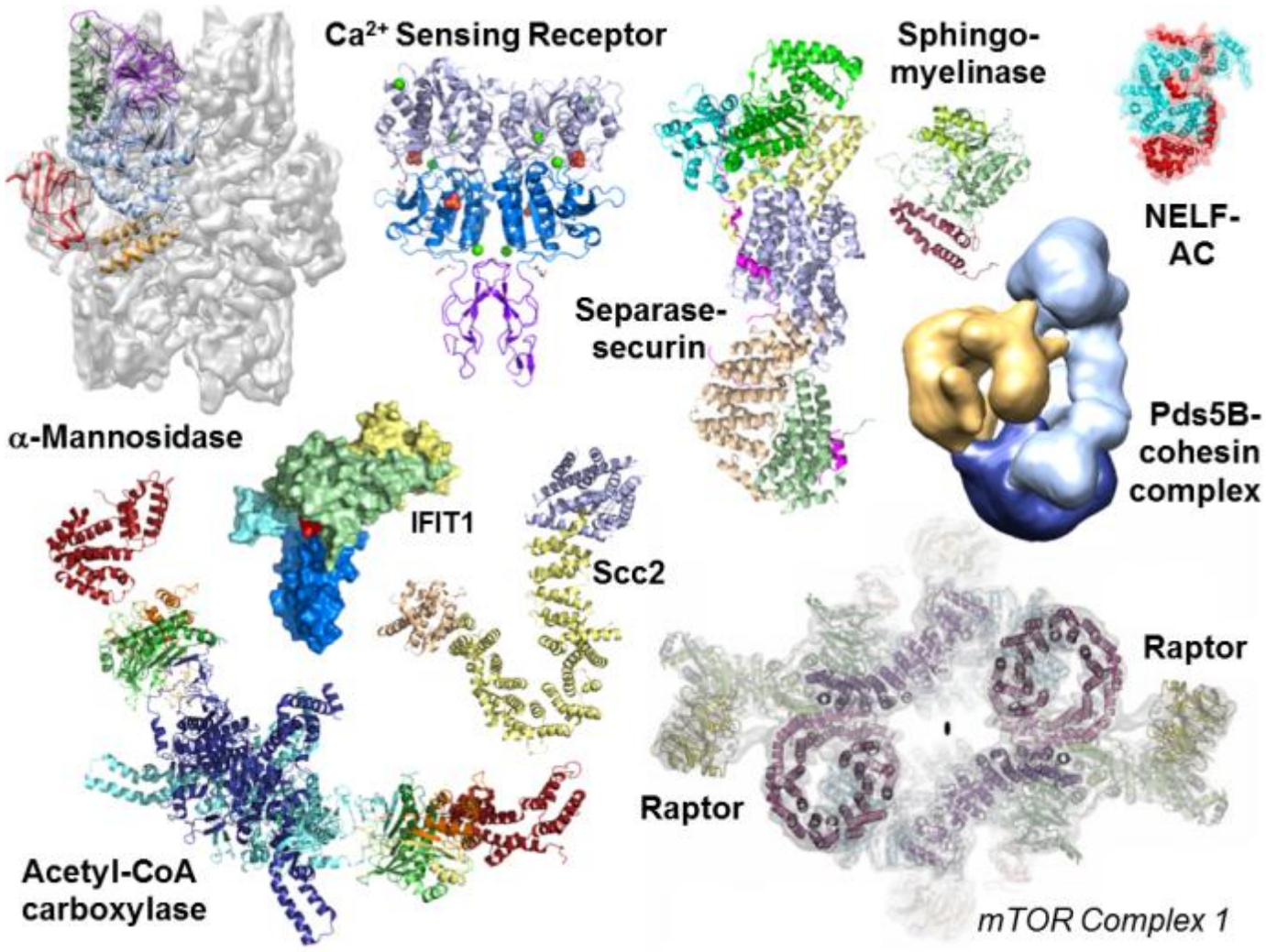
DNA Cargo: >150 kb

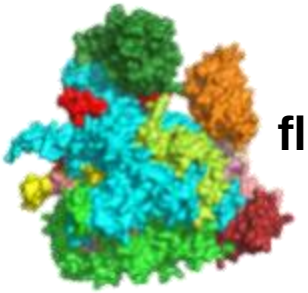
Bieniossek et al. **TiBS** 2012

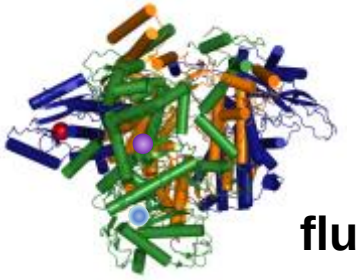
MultiBac Platform @ Berger Group: 100+ projects per year



MultiBac – Complex Production Technology



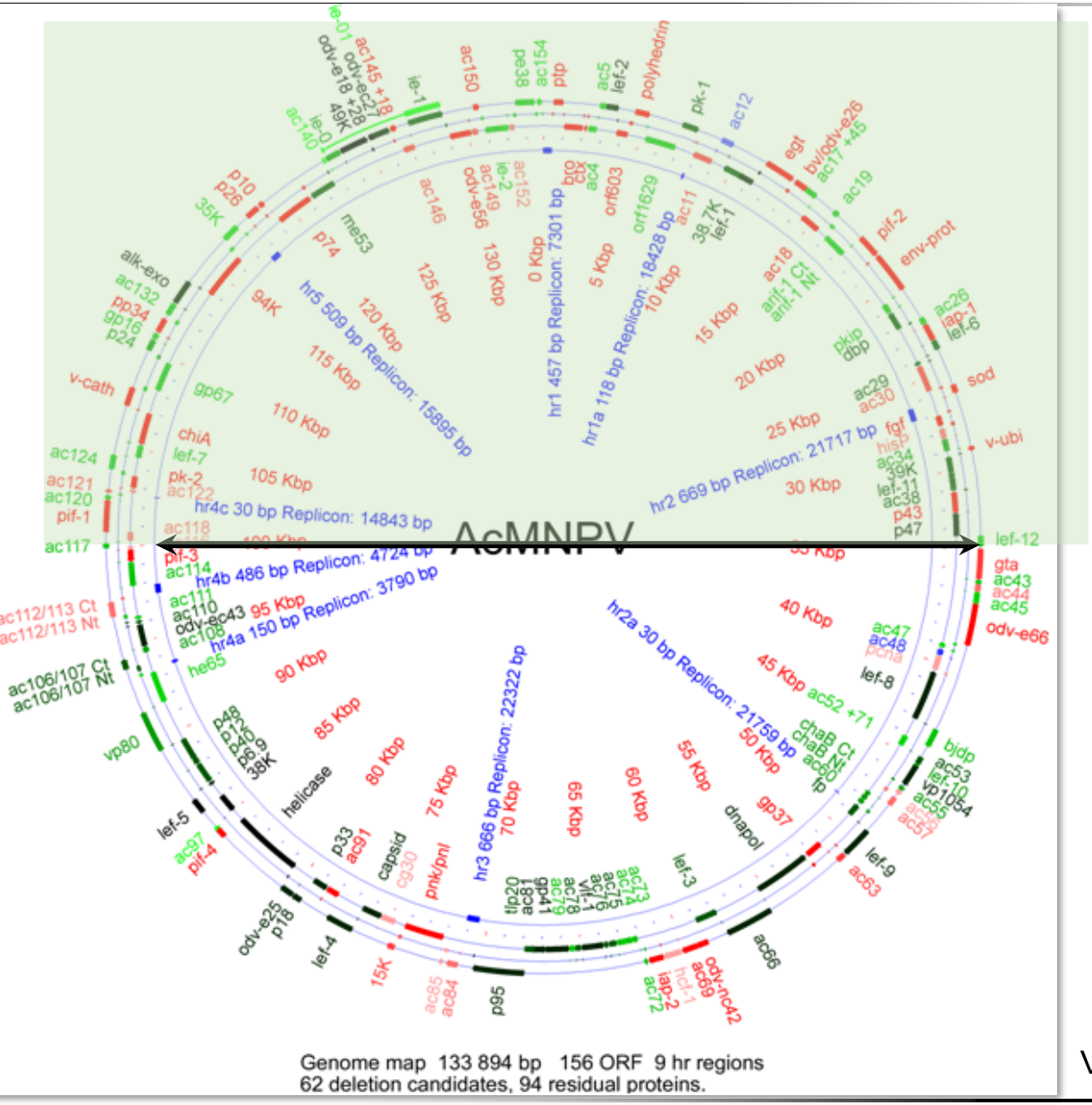




Pelosse et al. **BMC Biology** 2017

Reich et al. **Nature** 2014
Crepin et al.**COSB** 2015

Creating a Better BV Genome

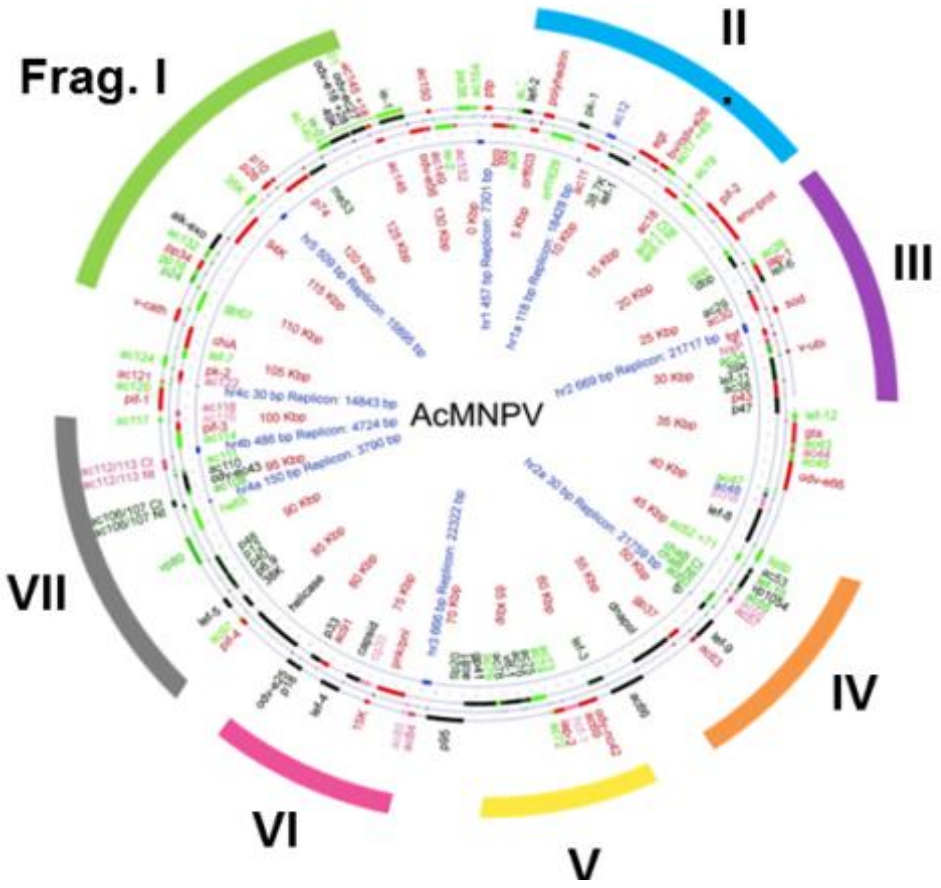


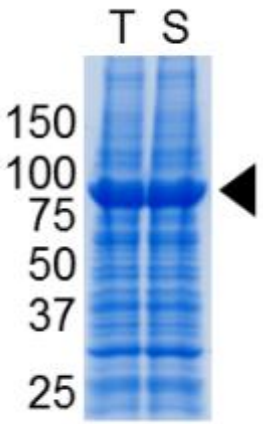
- Genome stability
- Autodeletion
- **Scale-up limitations**

36	Type 1: Deletion was published as tolerable.
10	Type 2: Deletion is likely harmless (loss in next neighbours or no mRNA).
10	Type 3: Deletion is perhaps harmless (loss in next neighbours).
6	Type 4: Deletion is perhaps harmless (variable gene lost in neighbours).
1	Variable in clade-I (no deletion category).
1	Variable in NPV (no deletion category).
3	Unique in AcMNPV.
16	Conserved in clade-Ib.
37	Conserved in clade-I.
12	Conserved in NPV.
28	Conserved in lepidopteran baculoviruses.
27	Core gene.
6	Core+ gene with conserved synteny.

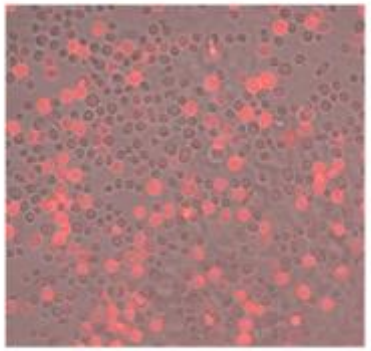
Vijayachandran et al.,**Bioengineered** 2013

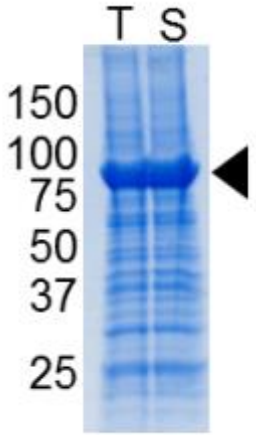
SynBac: Designing a Better BV Genome



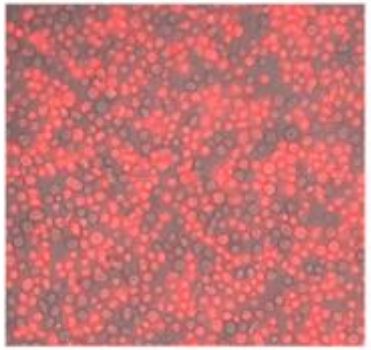


MultiBac



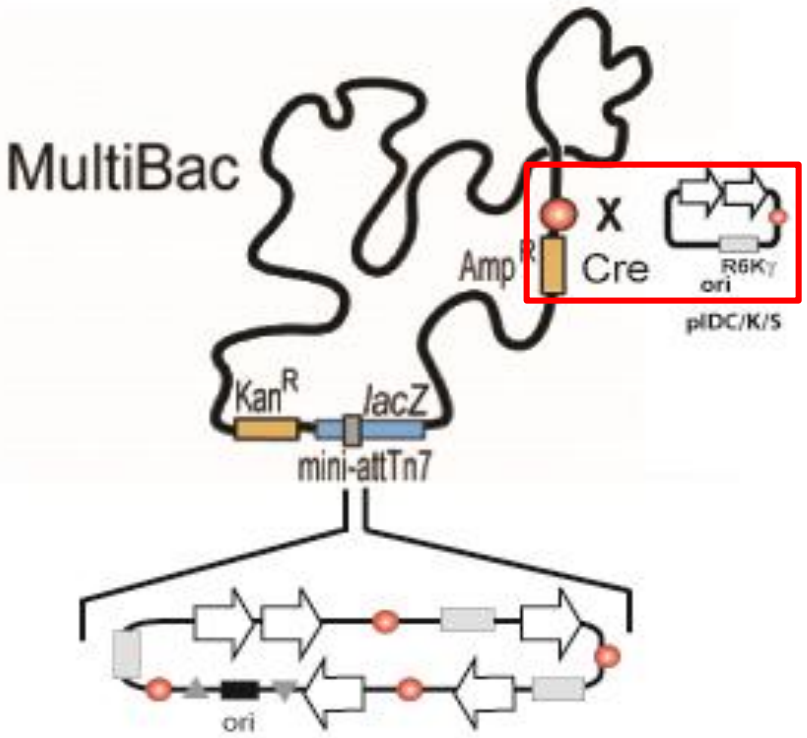


SynBac1.0



Pelosse et al.,**BMC Biology** 2017

Customized Baculoviral Genomes (SVNs)



Entry site on viral backbone facilitates functionalization

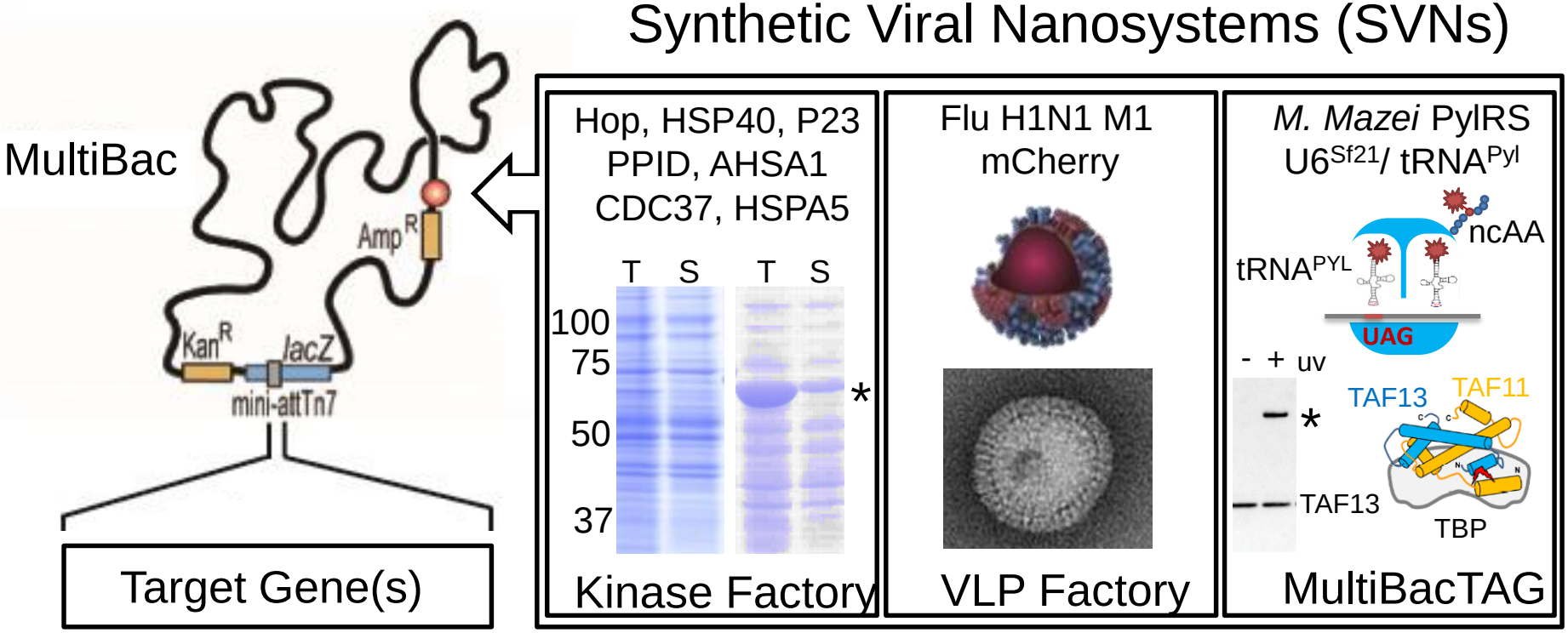
Tailored genomes with tailored properties

Complex INC

Synthetic Viral Nanosystems (SVNs) for:
Protein folding, High-content screening (HCS), Humanized Glcyosylation, Reprogramming, Genome Engineering, **VLP**s…

Customized Genomes

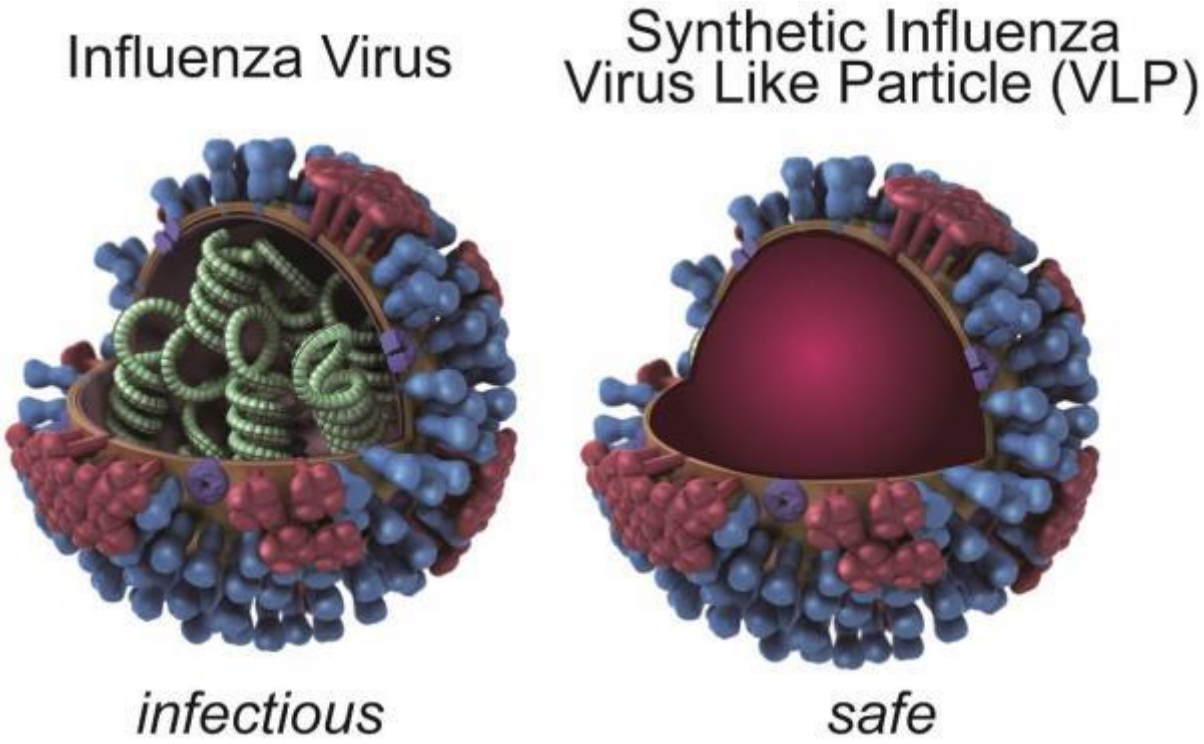
Synthetic Viral Nanosystems (SVNs)



Pelosse et al. **BMC Biology** 2017

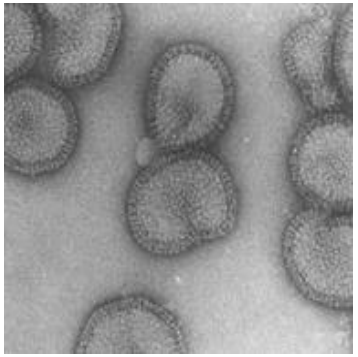
Influenza VLPs

VLP Factory: Influenza Virus-like particle array

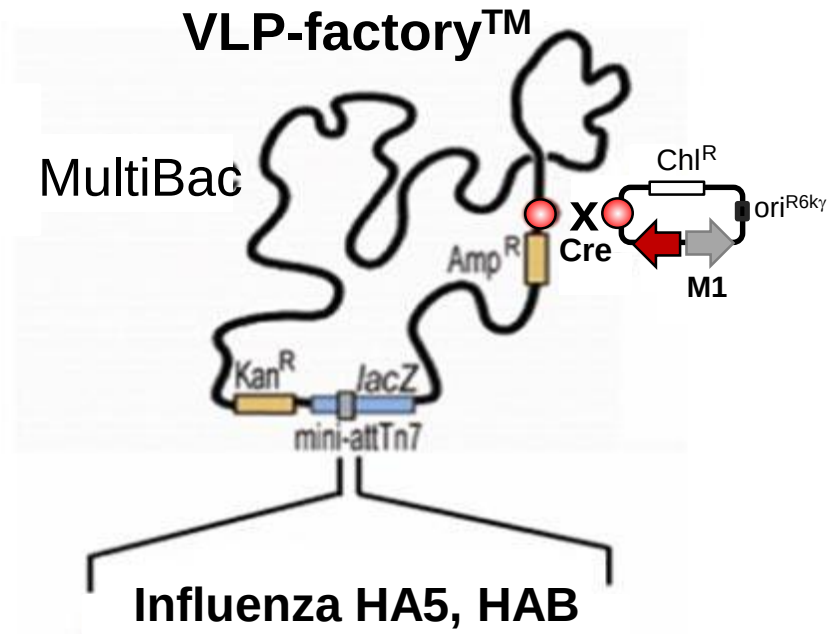


VLP Factory: Influenza Virus-like particle array

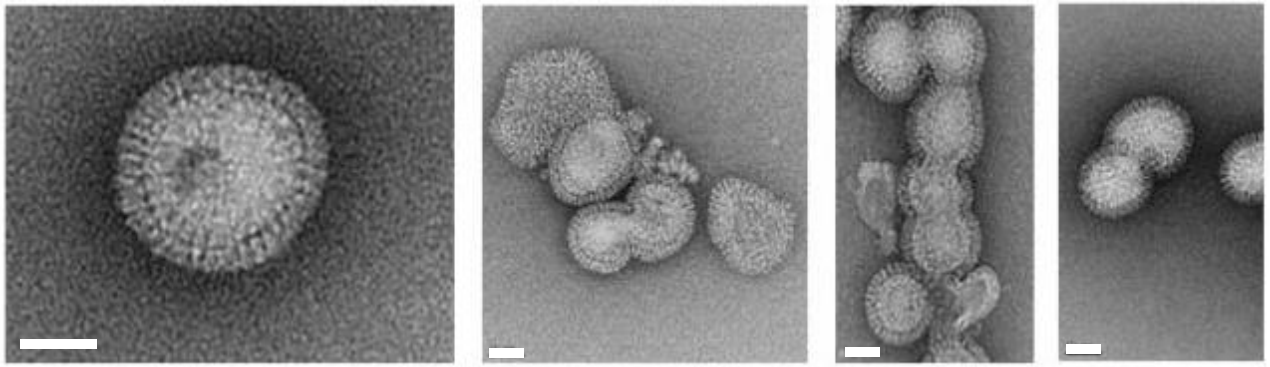
Live Influenza Virus



VLP-factory™



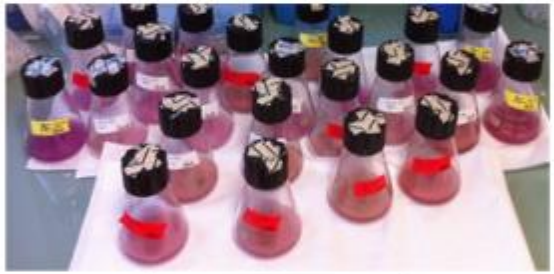
Influenza HA5, HAB



Sari-Ak et al.,**Meth. Miol. Biol.** 2018

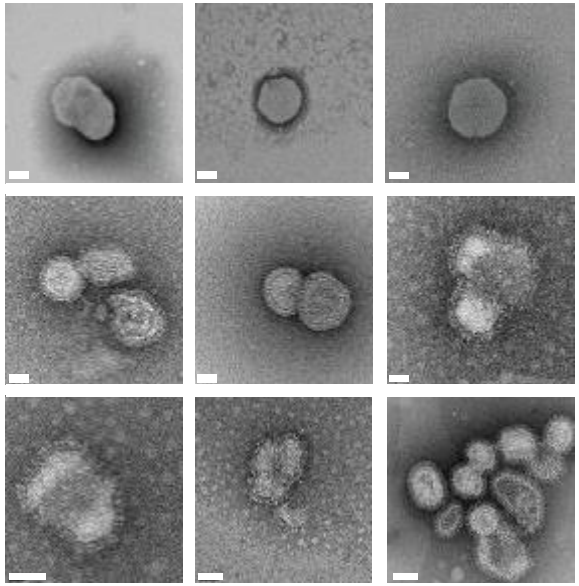
VLP Factory: Influenza Virus-like particle array

Influenza VLP array of HA wild-type and mutants in VLP-factory™



Small-Scale Purification
- Sedimentation
- Gradient Centrifugation

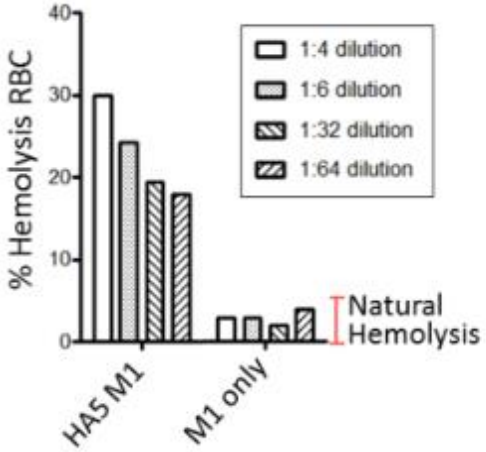
Functional Assays
- Hemolysis
- Animal models

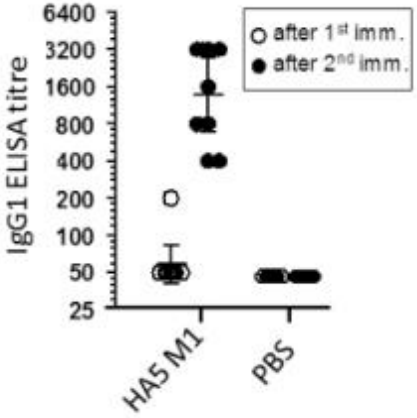


M1 only

HA5 M1

HAB M1





redbiotec (CMV)

University of BRISTOL

The ADDomer

Emerging infectious disease: Chikungunya

2025: FRANCE

5 Billion Euros!

2006: La Réunion

Cost of epidemic: 65 M €

- **Humanitarian consequences**
- **Economic consequences**
- **No efficient treatment**
- **No prophylactic vaccine**

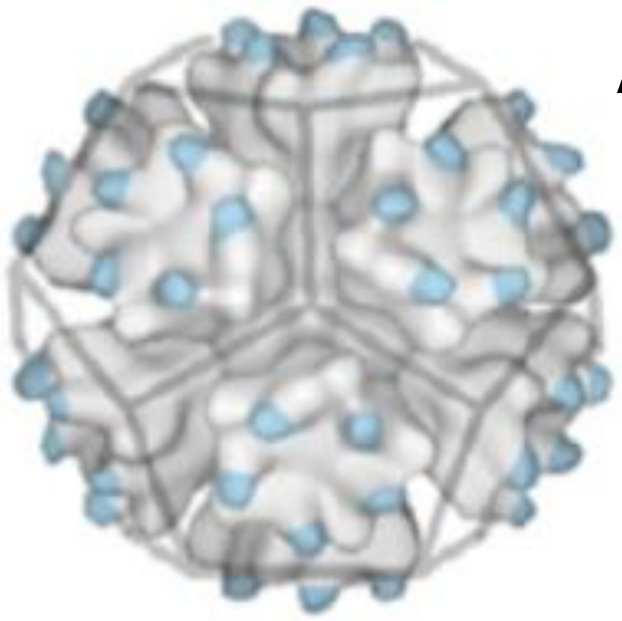
Medical check-ups:	17 M €
Medication	8 M €
Hospitalization	10 M €
Economic shortfalls	30 M €

Source: CHU La Reunion

Our technology: The ADDomer

Adenovirus is the most widely used viral vector in clinical trials (FDA approved).

- **We discovered a SINGLE COMPONENT of human Adenovirus that spontaneously forms a superparticle, the ADDomer.**
- **ADDomer is exceptionally suited for multi-epitope peptide/protein display to combat a wide range of diseases.**



ADDomer:

- ✓ **Synthetic protein scaffold**
- ✓ **Safe (no DNA/RNA inside)**
- ✓ **Thermotolerant (no cold chain)**
- ✓ **Scalable**
- ✓ **Highly soluble (high dose)**
- ✓ **Broad range of applications**

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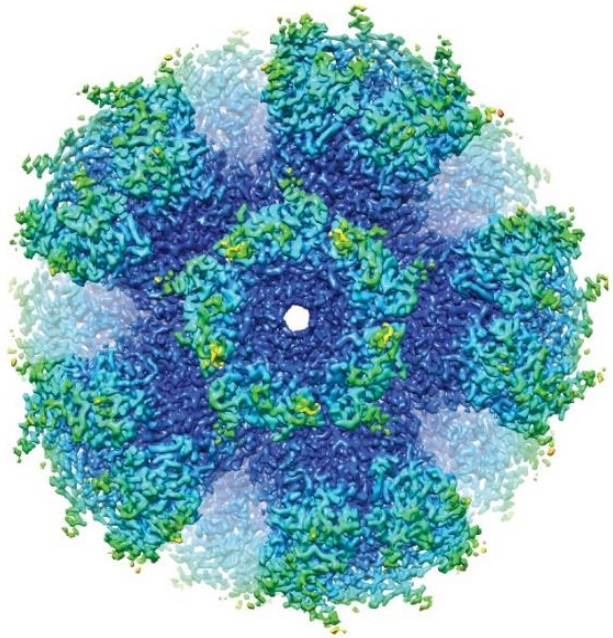

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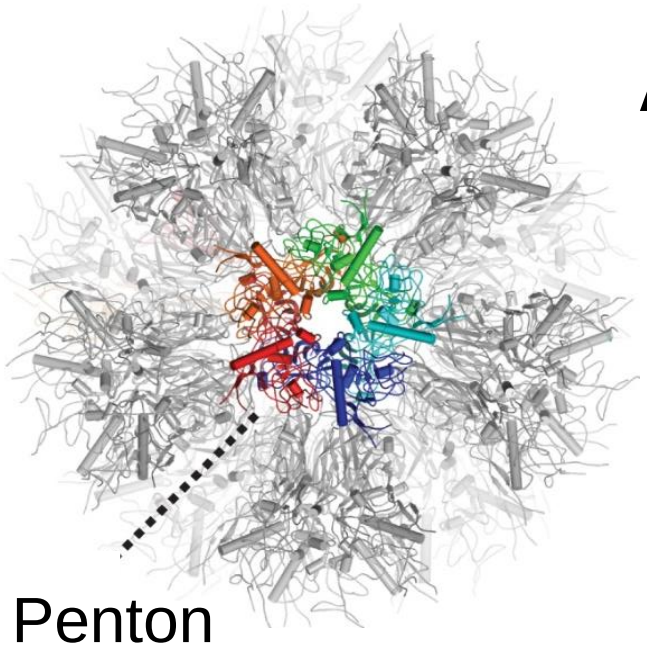

Penton

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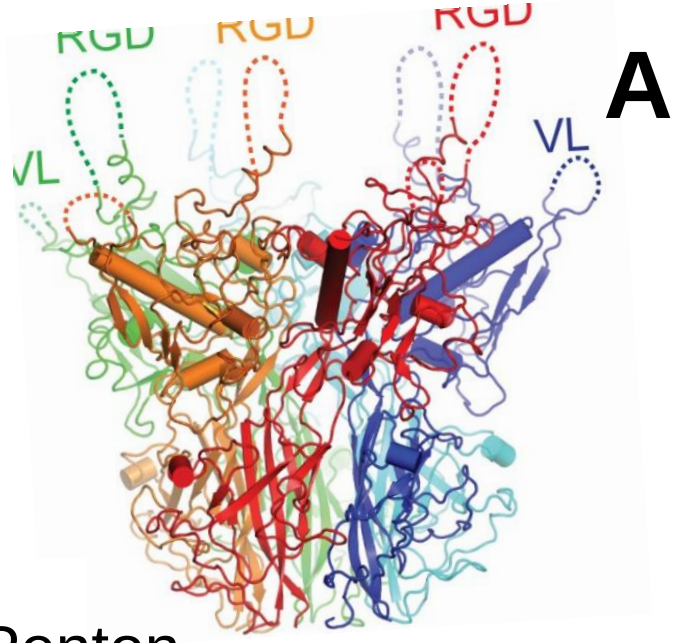

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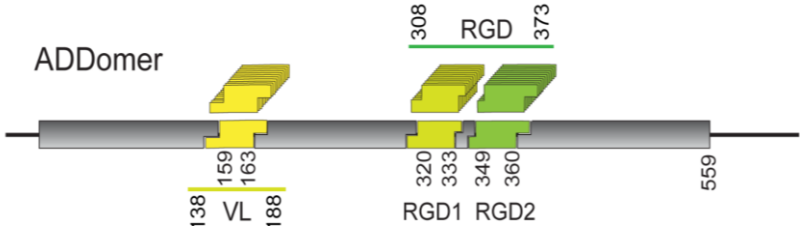
- ✓ Broad range of applications

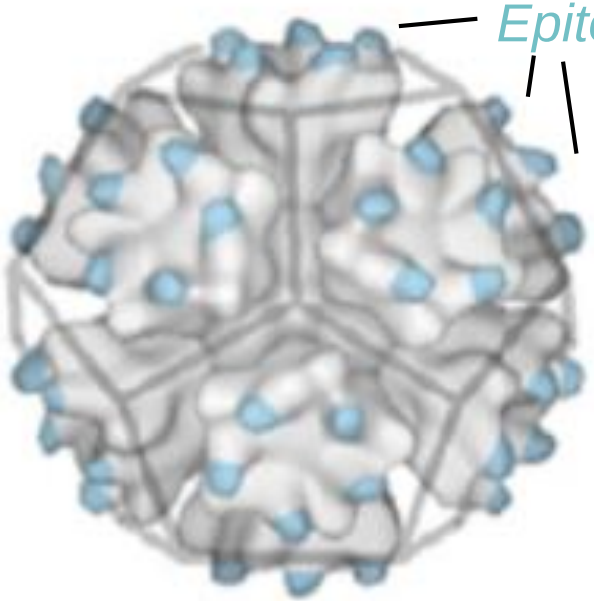
Our technology: The ADDomer

University of BRISTOL

‘Plug-n-play‘



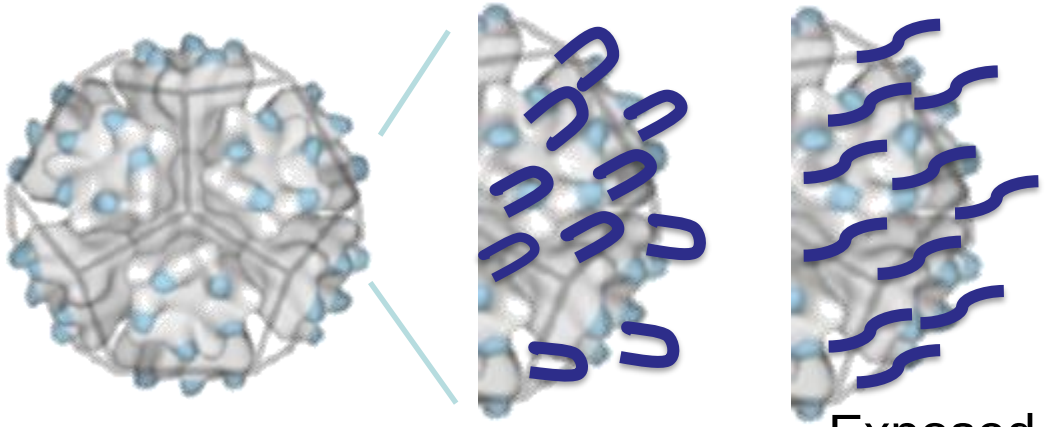
Designer Gene



One ADDomer displays up to 360 epitopes

Customizing ADDomer: Vaccines

Immunogenic epitope
(i.e. Chikungunya neutralizing antigen)

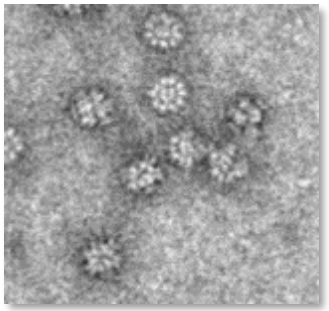


Constrained

Exposed
(nature-like)

ADDomer-CHIK:

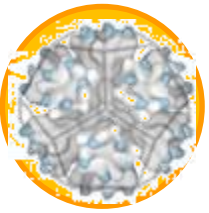
ADDomer displaying nature-like ‘exposed’ neutralizing peptide antigen epitope (120 copies per ADDomer)



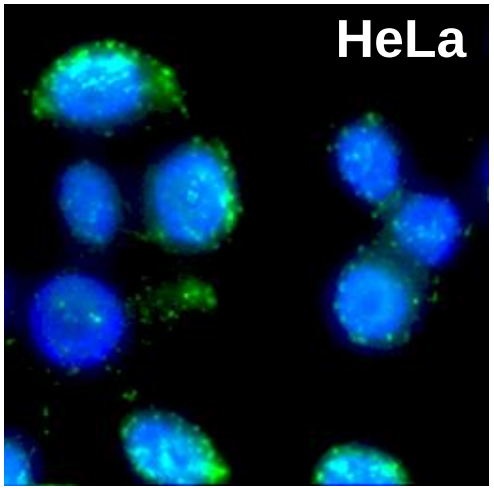
ADDomer-CHIK by EM

ADDomer: Chikungunya Vaccine Candidate PoC

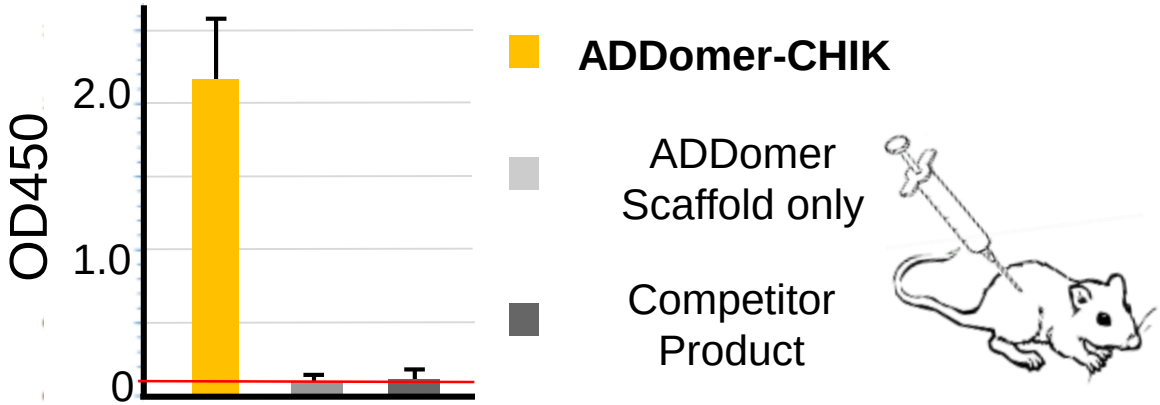
Chikungunya Immunization



ADDomer-CHIK
(120 copies, ‘exposed’ neutralizing CHIK epitope)



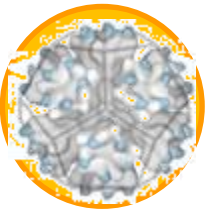
Efficient internalisation
(ADDomer-CHIK)



Strong humoral response
(Prime/Boost)

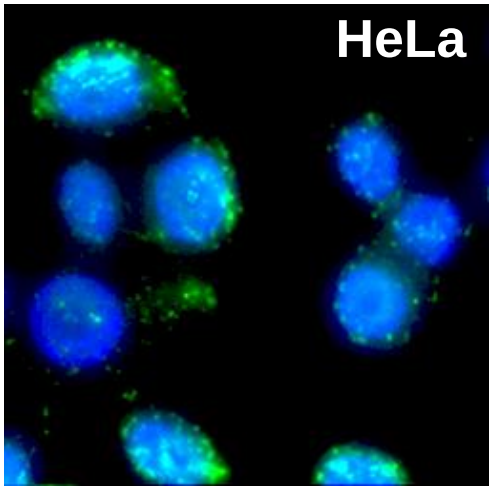
ADDomer-CHIK vaccine candidate confers <u>robust immune response</u> in mice and <u>outperforms competitor</u> product !

ADDomer: Chikungunya Vaccine Candidate PoC

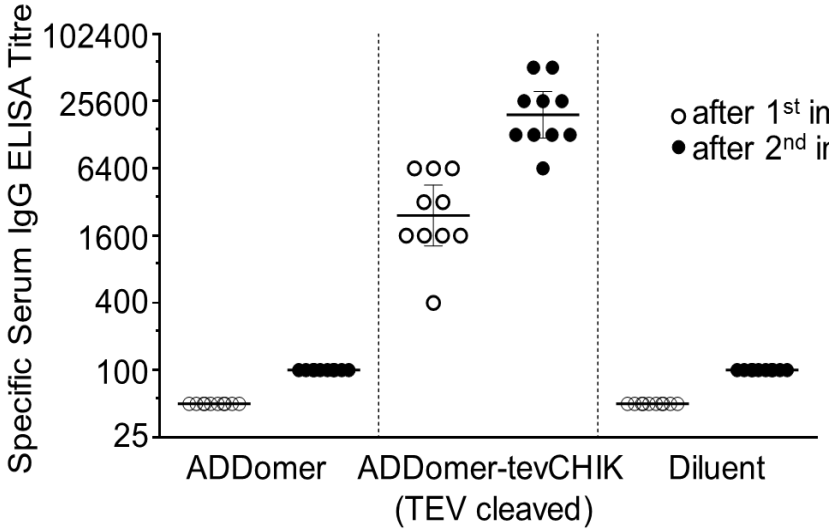


ADDomer-CHIK
(120 copies, ‘exposed’ neutralizing CHIK epitope)

Chikungunya Immunization



Efficient internalisation
(ADDomer-CHIK)

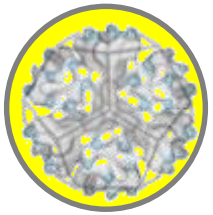


Strong humoral response
(Prime/Boost)

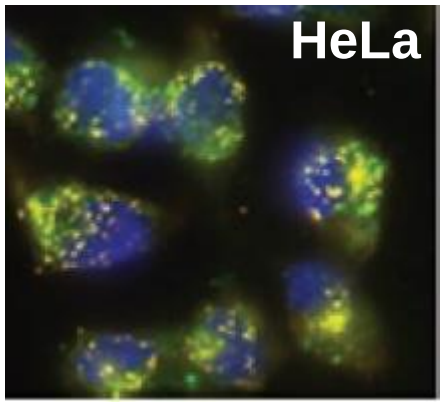
ADDomer-CHIK vaccine candidate confers robust immune response in mice and outperforms competitor product !

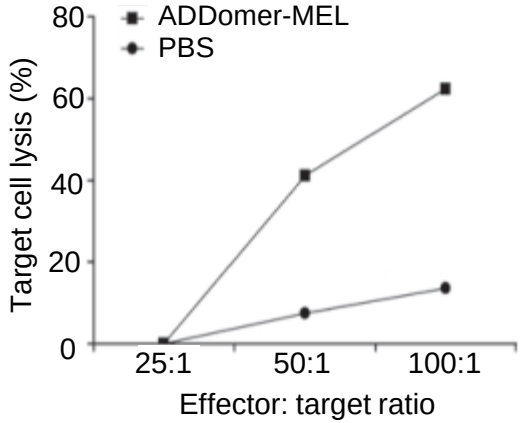
Application 2: Skin Cancer Vaccine

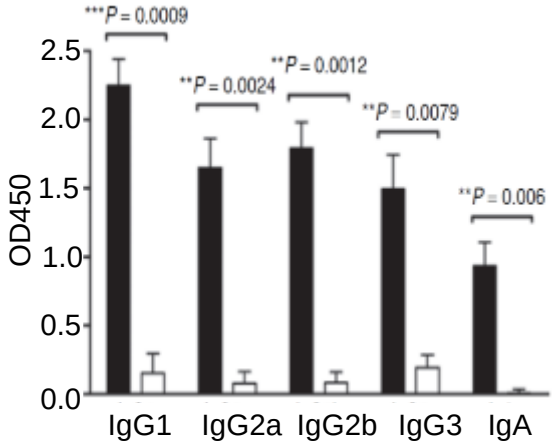
Melanoma (skin cancer) mouse model



ADDomer-MEL
(120 copies, melanoma model peptide epitope ‘ova’)







Efficient
internalisation

Specific
cellular response

Robust
humoral response

ADDomer-MEL vaccination achieves >90% tumour clearance!

The Berger Group



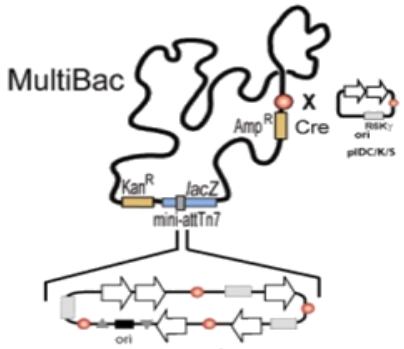


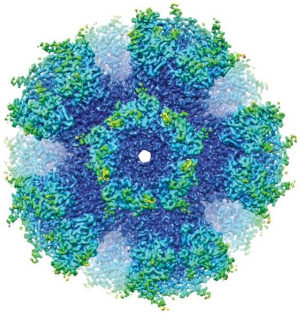


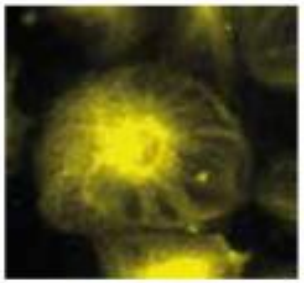
Alice Aubert
Francesco Aulicino
Shervin Bahrami
Itxaso Bellon
Christoph Bieniossek
Julien Capin
Maxime Chaillet
Hannah Crocker
Petra Drnkova
Fred Garzoni
Basia Gorda
Charles Grummit
Kapil Gupta
Matthias Haffke
Jannah Jeon
Isai Kandiah
Paul Lamaire
Jackwee Lim
Yan Nie
Martin Pelosse
Fruzsina Rabi
Duygu Sari-Ak
Catarina Silva
Thomas Taylor
Christine Tolzer
Deepak Thimiri
Simon Trowitzsch
Cristina Viola

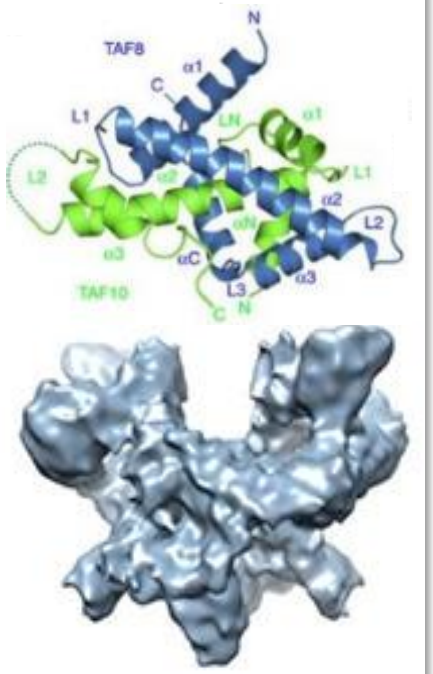
C. Schaffitzel
J. Bufton
Ian Collinson
M. Dillingham
C. Woods
M. Williams
M. Timmers (UMCU)
D. Hart (CNRS)
R. Ruigrok (UVHCI)
U. Schlattner (UJF)
P. Schultz (IGBMC)
G. Papai (IGBMC)
L. Tora (IGBMC)
C.V. Robinson (Oxford)
E.D. Laue (Cambridge)
J. Rappsilber (Berlin)
L. P. Serrano (CRG)
Christina Kiel (CRG)
T.J. Richmond (ETHZ)
Pascal Fender (IBS)
C. Vragnieau (IBS)
Phil Bates (Oracle)
Jenny Tsai (Oracle)
L. Mayr (GE Healthcare)
R.Roth (Astra-Zeneca)
R. Thoma (Roche)
J.P. Carralot (Roche)
D. Fitzgerald (Gen Biotech)

Thank you !









European Commission

wellcome trust

BBSRC

University of BRISTOL

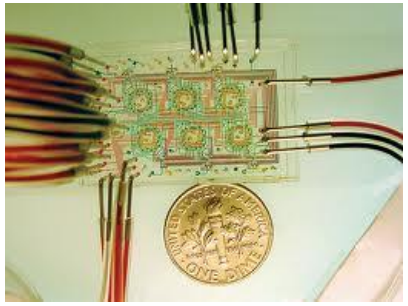
Thank you !

BrisSynBio
biomolecules to biosystems
from understanding to design

wellcome trust

HT Biology

Microfluidics



HPC

Cryo-TEM/DED

Join us - have fun !

imre.berger@bristol.ac.uk