BMEI-2022 Research :

WHO = World Health Organization

ICD = International Classification of Diseases

MOA = Mechanism of Action

POC = Proof of Concept

API = Active Pharmaceutical Ingredient

FF = DP = Final Formulation = Drug Product

QC = Quality Control

November 11, 2022

Dmitry Kulish

Skoltech

BMEI STRUCTURE AND TOPICS

- MONDAY
  - mentoring by request
- TUESDAY
  - lecture of the topic of the week
    - Indication + MOA + POC
    - Patent
    - Formulation + Manuf + QC
    - Reg guidances + Preclin + Clin
    - Value chain + Value delivery
- THUR
  - mentoring by request
- FRIDAY
  - Team presentation
    - **Last course activity day: Wed Dec 16th**

		TUE-FRI 9-12	
week 1	1	Onco/Tobacco game + BMEI course intro	
	4		
week 2	8	ELP	
	11	LECT: Indication + POC experiment + charact	
week 3	15	PRESO: Ind + POC experiment + valid QC	Michail Grubman
	18	LECT: Grubman	Michail Grubman
week 4	22	LECT: PATENT	
	25	PRESO: PATENT three claims	
week 5	29	LECT: Reg + Guidances + Preclin + Clin	
	2	PRESO: Reg + Guidances + Preclin + Clin	Sophia Yartseva
week 6	6	LECT: Formulation + Manuf + QC release	Sophia Yartseva
	9	PRESO: Formulation + Manuf + QC release	
week 7	13	LECT: BMEI career	
	16	FIN PRESOS	Michail Grubman

Innovation is done in cross-disciplinary and cross-cultural teams

- Hence Skoltech must give you cross-disciplinary cross-cultural experience
- Teams to be founded next Monday must be:
  - cross-disciplinary: **maximum** 1 (one) LS student per team
  - multi-cultural: **minimum** two different nationalities or CREIs
  - multi-gender: **minimum** two genders
- Carefully select your team next week !
  - Experience of working in a good team is priceless
    - Experience of working in bad team is also important
- **START SCREENING OUR EXCEL TABLE for your ideal team !**

BMEI Team Cooperation Policy

- BMEI TEAM:
  - 4 (four) students
  - Defined roles
    1. MOA & POC
    2. QC & Patent
    3. Preclin + Reg + Clin
    4. Manuf + QC
  - Joint presentations
    - Each team will present several times on different topics
    - Each team member must present min 1 minute part of the presentation
- Team may request increasing/decreasing your BMEI class participation score
  - *It happens every year after serious discussion*

TEAM FORMATION: TWO STEPS

- Friday Nov 11: Initial team Formation
  - **Hunch & Fit (**general E&I experience**)**
- **Monday Nov 14, 11pm:**
  - **Each BMEI student submits team presentation with team names list at the 1st slide**
- Tuesday Nov 15: 1st Project presentation
  - **Does it hold water ? (**with Mikhail Grubman**)**
- Friday Nov 18: general BMEI talk from Mikhail Grubman

BMEI PROJECT STRUCTURE

- **RESEARCH**
  - Indication
    - Exactly which disease you treat or prevent
  - MOA = Mechanism of action
    - Science
  - POC = Proof of Concept
    - Technology & Prototype
  - Patent claims
- **DEVELOPMENT**
  - Formulation = Consumer device
    - Exactly what is received by the patient
  - QC = Quality Control = Validation
    - You have to know what you give to people
  - Manufacturing
    - rawmats, equipment, processes
- **REGULATORY**
  - Regulatory guidances & Sci Publications
  - Preclinical design
  - Clinical design
  - Value delivery chain

		TUE-FRI 9-12	
week 1	1	Onco/Tobacco game + BMEI course intro	
	4		
week 2	8	ELP	
	11	LECT: Indication + POC experiment + charact	
week 3	15	PRESO: Ind + POC experiment + valid QC	Michail
	18	LECT: Grubman	Michail
week 4	22	LECT: PATENT	
	25	PRESO: PATENT three claims	
week 5	29	LECT: Reg + Guidances + Preclin + Clin	
	2	PRESO: Reg + Guidances + Preclin + Clin	Sophia Y
week 6	6	LECT: Formulation + Manuf + QC release	Sophia Y
	9	PRESO: Formulation + Manuf + QC release	
week 7	13	LECT: BMEI career	
	16	FIN PRESOS	Michail

THE PROBLEM STATEMENT

Tue, Nov 15th : the 1st graded assignment presentation

- Slide 1. INDICATION:
  - WHO ICD = World Health Organization International Classification of Disease = МКБ
  - diagnostics & incidence & prevalence
  - current WHO-recommended treatment/alternative
  - impact of your innovation (efficacy, toxicity, convenience, cost)
- Slide 2. MOA + FF + QC:
  - MOA (Scientific Rationale)
  - Formulation or Technical description
    - Basic simple QC for COM
    - Basic TD/validation for devices/services
- **Slide 3: POC experimental design:**
  - **rationale**
  - **materials and methods**
  - **negative control**
  - **positive control (comparable/benchmark)**
  - **statistics**
- **Slide 4: POC experiment results and discussion**
  - **raw data comprehensively presented**
    - yes, it may be artificially created (FITUMI is not exactly falsification)
  - **discussion**
  - **conclusions**
- Slide 5. TEAM ROLES:
  1. MOA & POC
  2. QC & Patent
  3. Preclin + Reg + Clin
  4. Manuf + QC
- **You submit your slides for grading in Canvas on next day noon after the presentation**

BioMed PSC illusions and pains

SLIDE 1:

- **WHO ICD**
  - diagnostics
  - incidence
  - prevalence
- **current WHO-recommended treatment/alternative**
  - **impact of your innovation**
    - efficacy
    - safety
    - quality of life
    - compliance

- **Everybody needs cancer cure (remember PD-1 game)**
  - Patient
    - Not only cure, but also social fairness and quality of life
  - Doctor
    - Efficacy and safety
  - Pharmacologist
    - Not only cure, but also stability of the formulation
  - Manufacturer
    - Not only cure, but also manageable technology + forecast of demand
  - Distributor
    - Not only cure, but also sales volume

DO YOU EXPECT ME TO LEARN MYSELF WHAT IS POC & QC IN BIOMED? AND HOW TO DO PRECLINICAL STUDIES FOR CERVICAL CANCER?

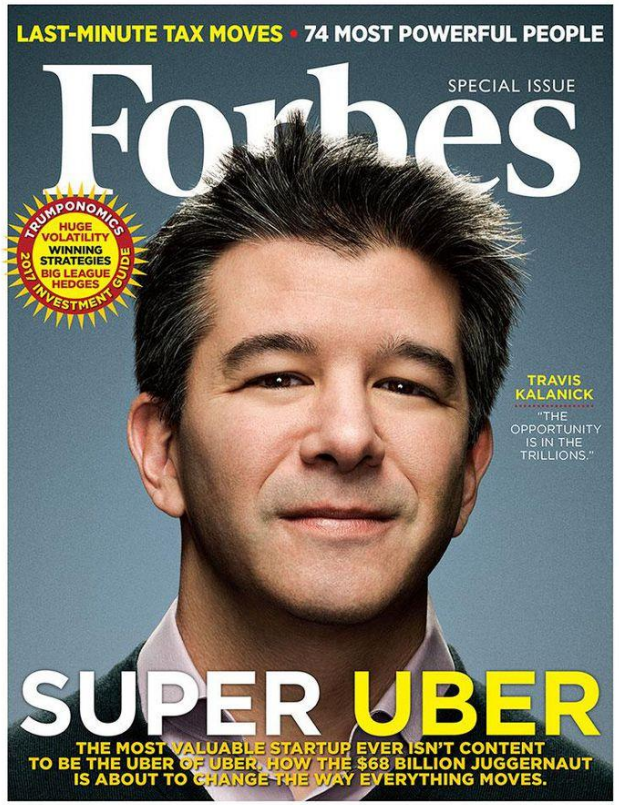
- **Yes!**
  - Because MOA and QC for each project is unique and general lecture is meaningless – that is the concept of empirical experiential learning = project-based education
  - Because that's how you will operate throughout your successful career – you will be daily bombarded by new urgent requests
- **How you do it**
  - Ask GOOGLE & SCHOLAR & PubMed
    - EVERYTHING is there ! You just need to try hard
  - Ask experts and doctors
    - Yes, it is all about soft skills
- **How to ask**
  1. State your name and team and topic
  2. State your assumption on the topic
  3. Ask whether it is correct

HBR: are you solving the right problem ?

- Step 1: Establish the Need for a Solution
  - What is the basic need?
  - What is the desired outcome?
- Step 2: Justify the Need
  - Who stands to benefit and why?
  - How will we ensure that a solution is implemented?
- Step 3: Contextualize the Problem
  - What approaches have we tried?
  - What have others tried?
  - What are the internal and external constraints on implementing a solution?
- Step 4: Write the Problem Statement
  - Is the problem actually many problems?
  - What requirements must a solution meet?
  - How will solutions be evaluated and success measured?

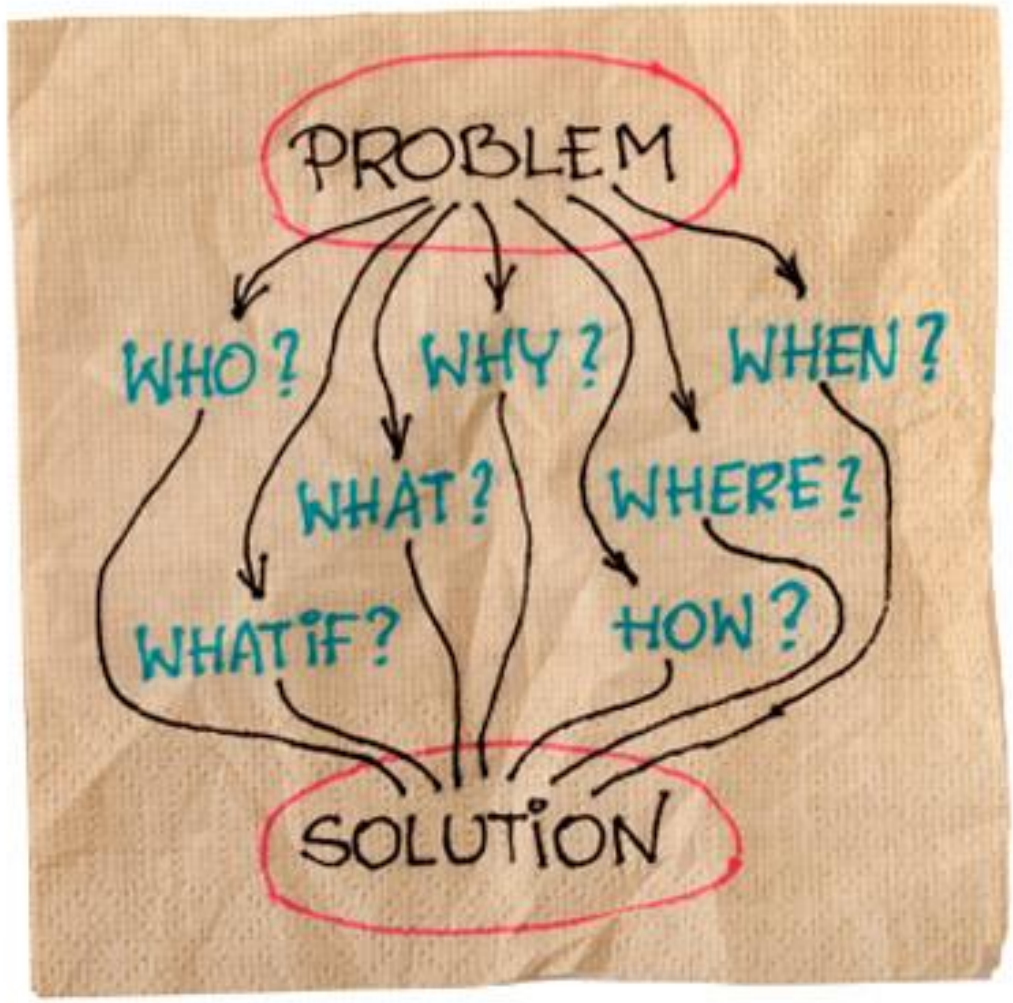
FORBES: Problems worth solving

- Green flags
  - Is there really enough waste that it can be considered a problem?
  - To what extent will this solution eliminate the waste/solve the problem?
  - Will this product/service create additional waste (of time, resources, energy, etc.) or additional problems?
  - Why hasn't anyone fixed this yet? (the story of the problem)
- Red Flags
  - Market-product fit rather than product-market fit
  - Defining inconveniences as problems
  - Masking social problems under the technological ones
  - Overpromising
- 4 routes to the problem
  - Use Strategy to Identify Problems
  - Reframe Existing Problems
  - Work Backward from a Far-in-the-Future Vision
  - Use Other Domains for Insight:



PSC is the best start

CONTEXT When does the problem occur? Every workday, in the mornings and evenings for an average of 2-3 hours per day	**PROBLEM** What is the root cause of the problem? Lose time in traffic instead of doing something more valuable	**ALTERNATIVES** What do customers do now to fix the problem? Sign up for Uber and accept rides only when going to or coming back from work
CUSTOMERS Who has the problem most often? Young men aged 25-35 with middle-low income, who live in suburban São Paulo and work in a corporate office in the city center	**EMOTIONAL IMPACT** How does the customer feel? Frustration & boredom **QUANTIFIABLE IMPACT** What is the measurable impact (include units)? Lose on average 40 hours per month	**ALTERNATIVE SHORTCOMINGS** What are the disadvantages of the alternatives? Driving for Uber requires more time waiting for a ride, as trip origin & destination might not coincide with their home-work itinerary



Slide 2: MOA
Empirical medicine is dead

- Non-targeted effect can not be engineered, enhanced, and personalized
- Empiric findings evolved from desirable to prohibited
  - MOA is the start of conversation, not the nice-to-have Christmas story
  - YODA is the engine of innovation
    - **In 19th century biomed innovation was driven by mad scientist with a smoking test tube**
    - **Today biomed innovation is the set of audited standardized (GLP, GCP) data chained to validated science (MOA)**
- Biotech Co is *de facto* department of Big Pharma carrying all risks of discovery

GRAPHICAL ABSTRACTS

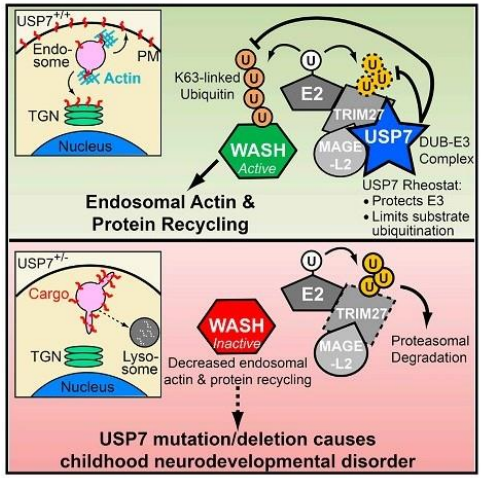
Skoltech Biomedical E&I, Dmitry Kulish, November 2021

Article

Molecular Cell

USP7 Acts as a Molecular Rheostat to Promote WASH-Dependent Endosomal Protein Recycling and Is Mutated in a Human Neurodevelopmental Disorder

Graphical Abstract



Authors

Yi-Heng Hao, Michael D. Fountain, Jr., Klementina Fon Tacer, ..., Margarita S. Saenz, Christian P. Schaaf, Patrick Ryan Potts

Correspondence

schaaf@bcm.edu (C.P.S.), ryan.potts@utsouthwestern.edu (P.R.P.)

In Brief

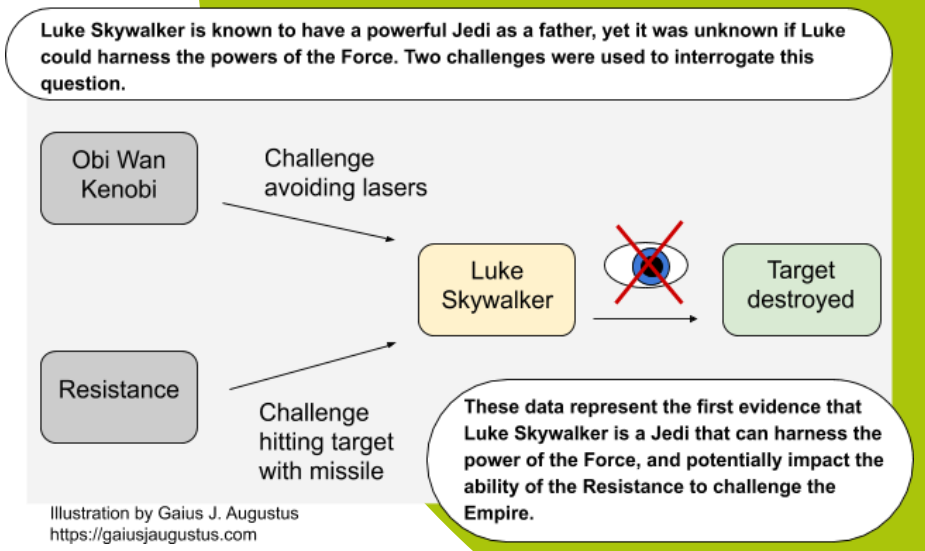
Hao et al. describe a function of the USP7 deubiquitinating enzyme in regulation of WASH/retromer-mediated endosomal protein recycling. USP7 functions as a molecular rheostat to prevent auto-ubiquitination and proteasomal degradation of TRIM27 E3 ubiquitin ligase, but also deubiquitinates WASH. Genetic studies identify cases of USP7 mutation/deletion resulting in a human neurodevelopmental disorder that overlaps with MAGE-L2 mutation.

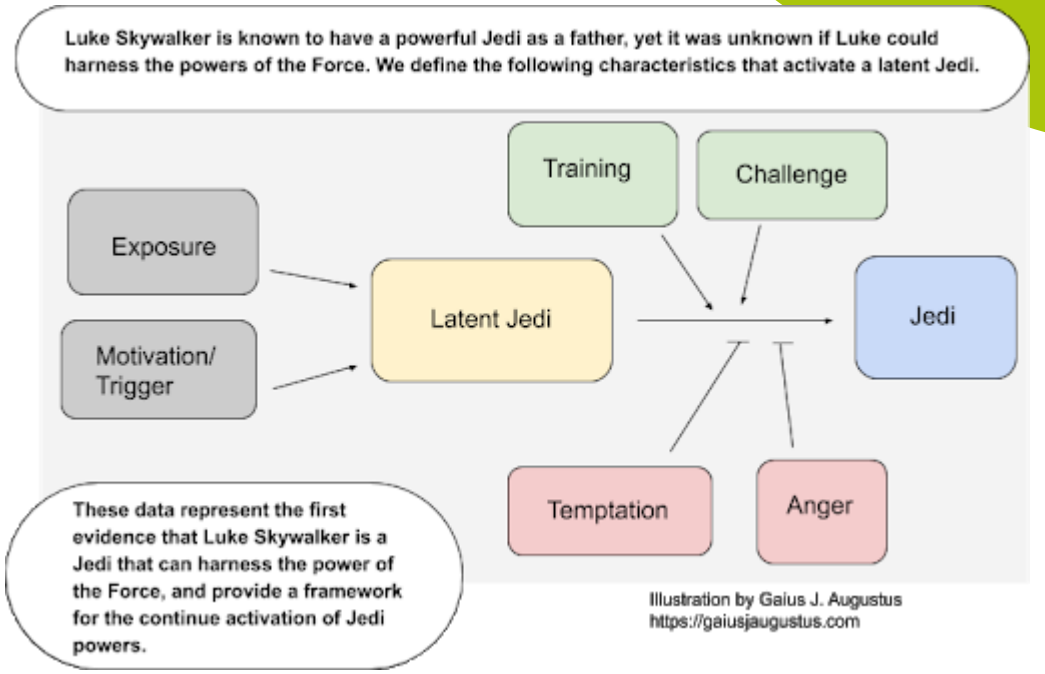
Highlights

- USP7 is part of the MAGE-L2-TRIM27 ubiquitin ligase and enables endosomal recycling
- USP7 protects TRIM27 from auto-ubiquitination and proteasomal degradation
- USP7 buffers WASH ubiquitination levels to maintain proper endosomal actin levels
- Mutation of USP7 causes a human neurodevelopmental syndrome, including autism

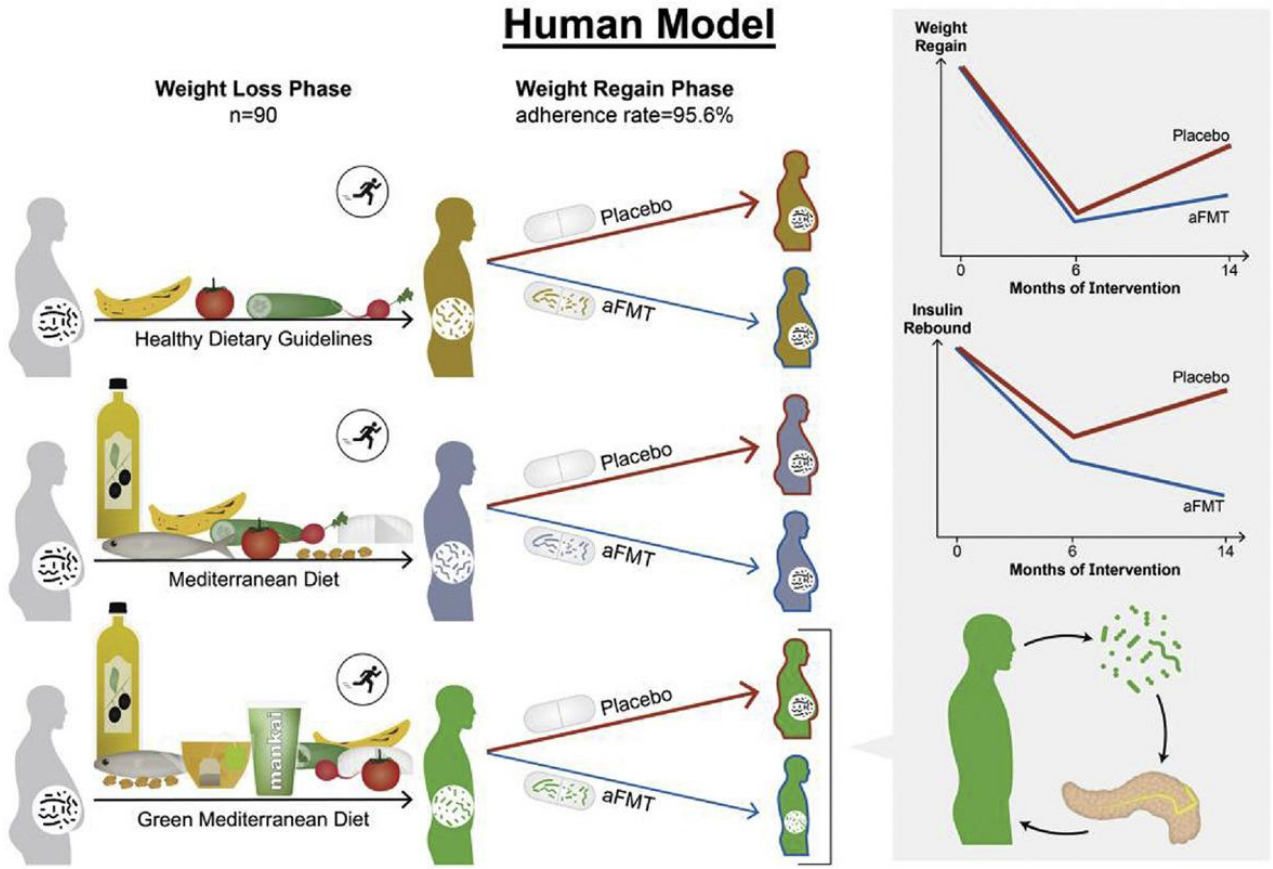
Hao et al., 2015, Molecular Cell 59, 1–14
September 17, 2015 ©2015 Elsevier Inc.
http://dx.doi.org/10.1016/j.molcel.2015.07.033

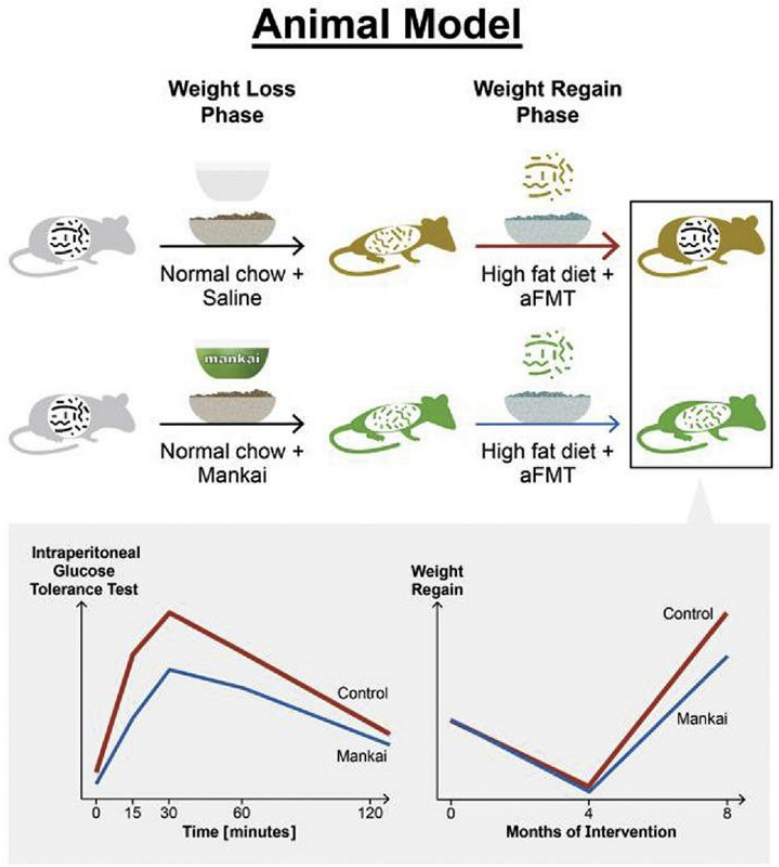
CellPress





GRAPHICAL ABSTRACTS





Gastroenterology

SLIDE 2. MOA starts with COMPOUND IDENTIFICATION or DEVICE VALIDATION

- Surprisingly many people start discussing the experiment without identifying the API (Active Pharmacological Ingredient) or validating the device
  - What exactly you are talking about ?

	STANDARD TECHNIQUE 1	ORTHOGONAL STANDARD TECHNIQUE 2	SPECIFIC ACTIVITY
Pharma QC	Most basic analytic technique, mostly HPLC nowadays	Spectroscopy or microscopy or else	Specific biological activity
Device/Service Validation	Single signal or event in the middle of the possible range	Absence of the signal under negative control conditions	Standard range of signals under the standard (control range) conditions

ALMOST POC and PRECLINICAL

SLIDE 3. EXPERIMENTAL DESIGN

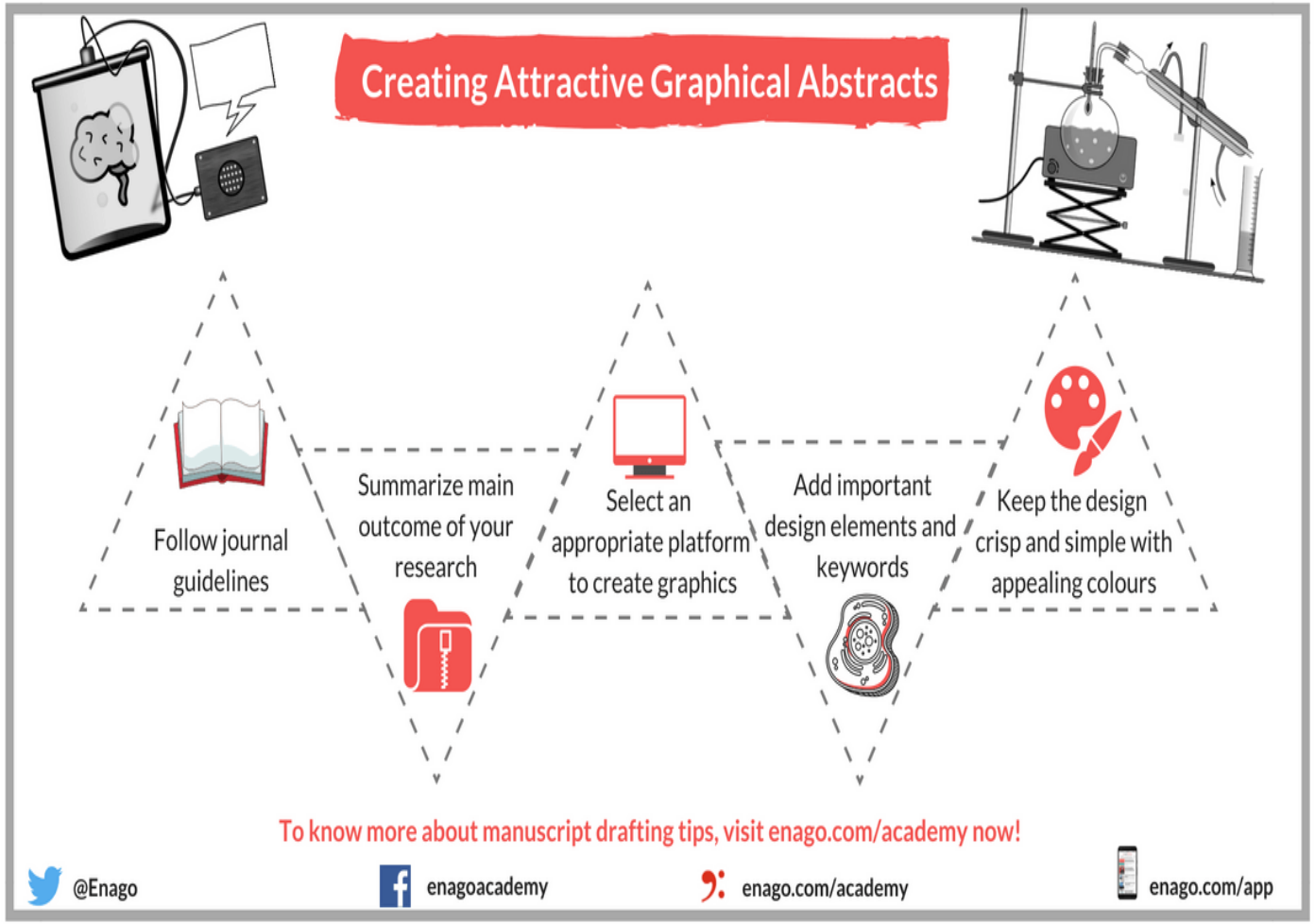
- Surprisingly few people can design the comprehensive experiment
  - **That is science !**
    - **rationale**
    - **materials and methods**
    - **negative control**
    - **positive control (comparable/benchmark)**
    - **Statistics**
  - How many agarose gel lanes you need for ideal experiment or PCR detection of Target DNA ?

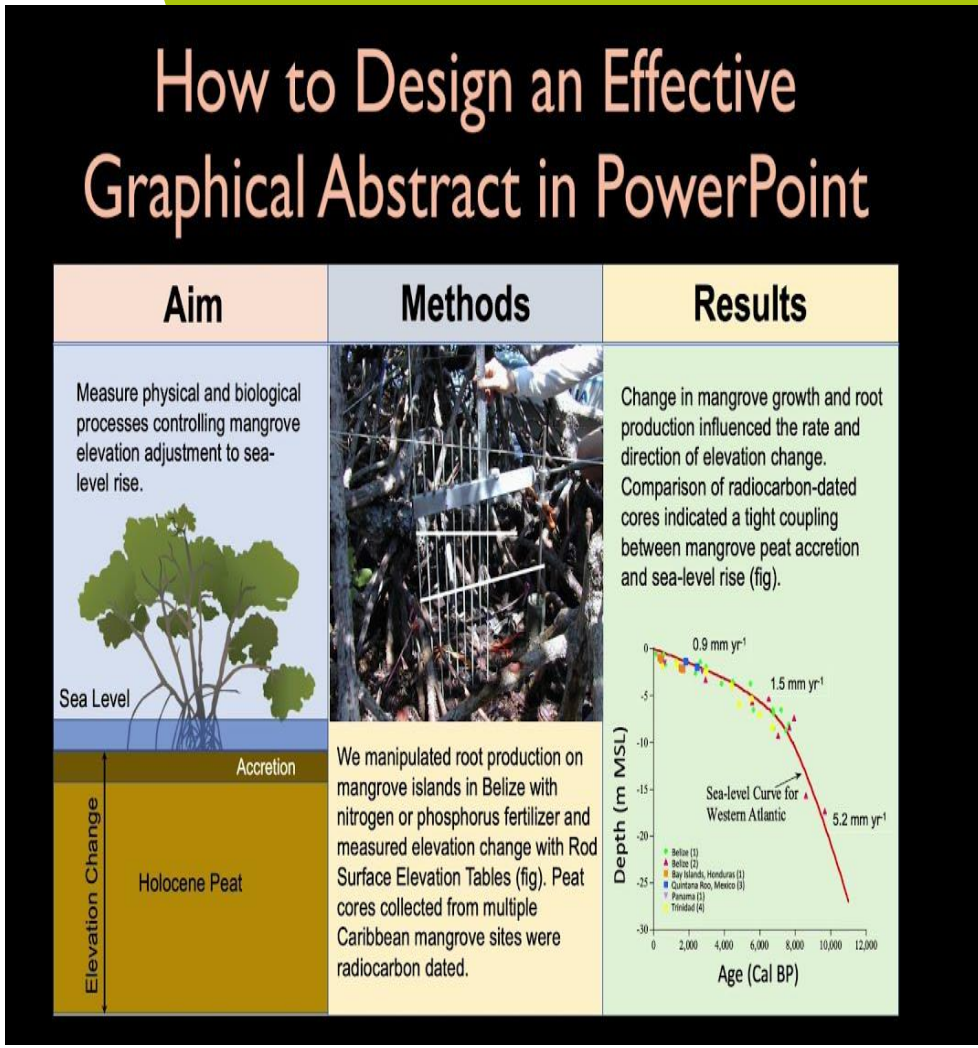
    - 1 – 2 – 3 – 4 – 5 – 6 – 7 - 8

SLIDE 4. RESULTS AND DISCUSSION

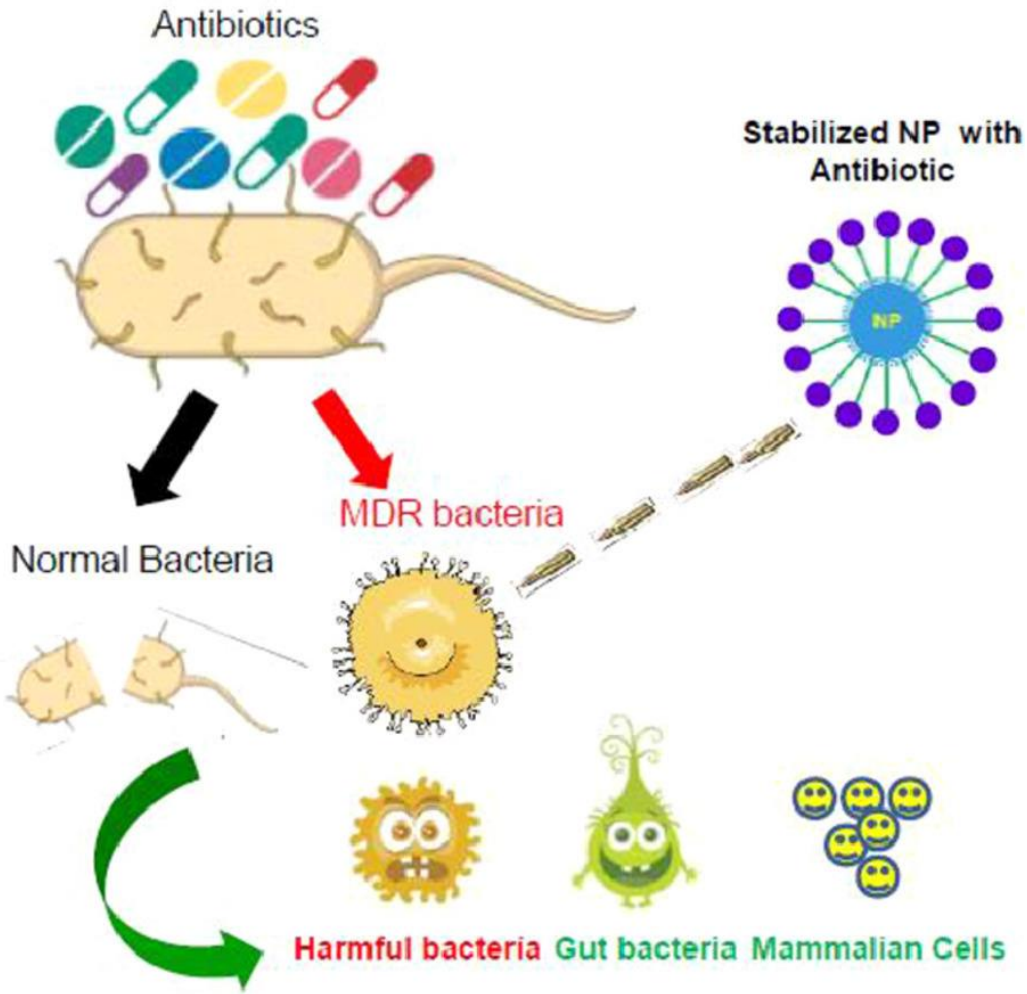
- Show crucial hard data
  - Yes, you may make it up
    - ***FITUMI is not exactly falsification though certainly borderline***
  - But do it professionally
    - No blind graphs
    - No unexplained symbols
    - Brief summary of the experiment (3) sentences
      - **CROWDED SLIDES are hated by managers but loved by scientists !**
- Discussion
  - We learned this, this, and that
- Conclusion
  - We conclude that this molecule/device/procedure provides the values of this, this, and that

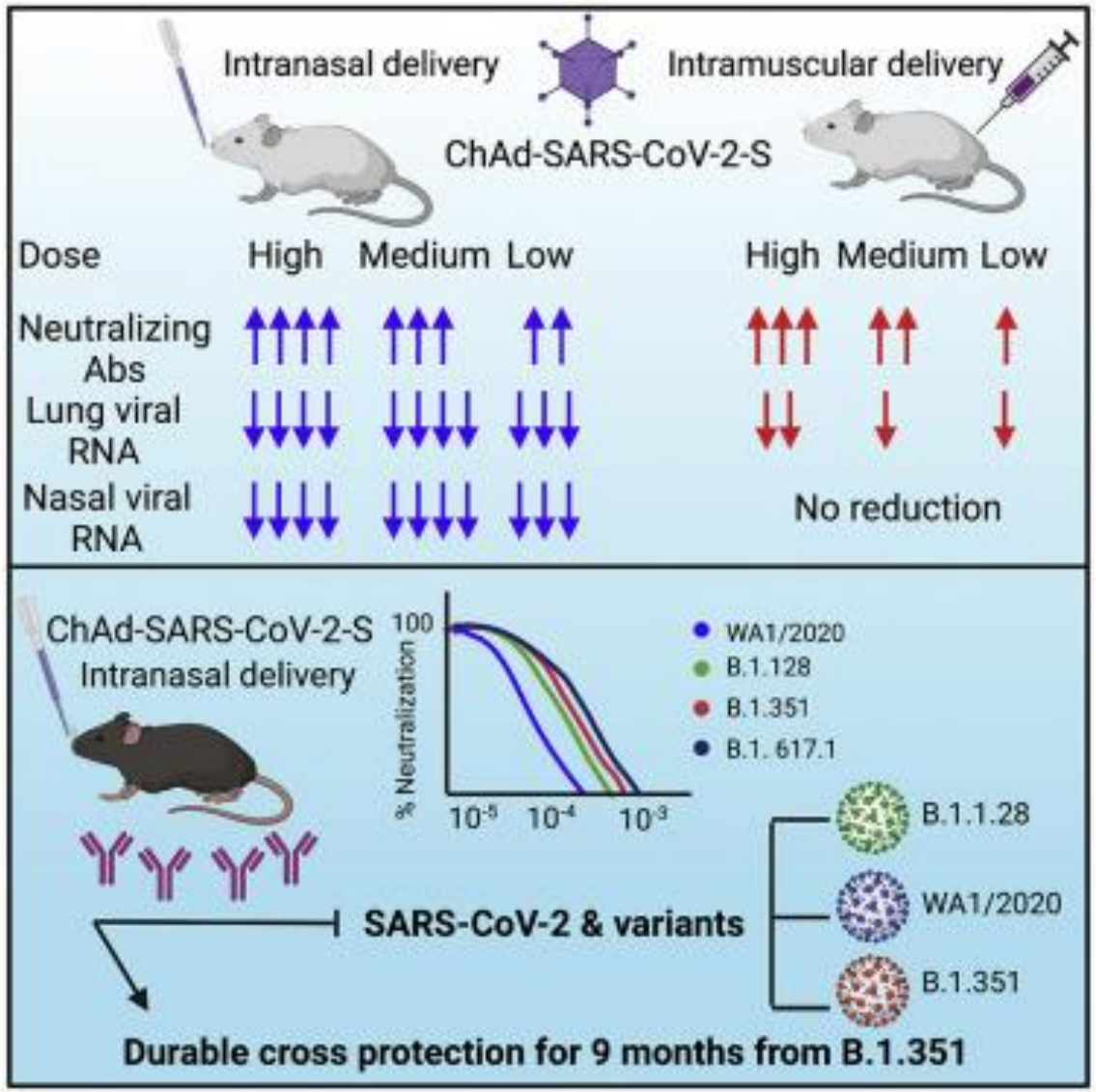
GRAPHICAL ABSTRACTS



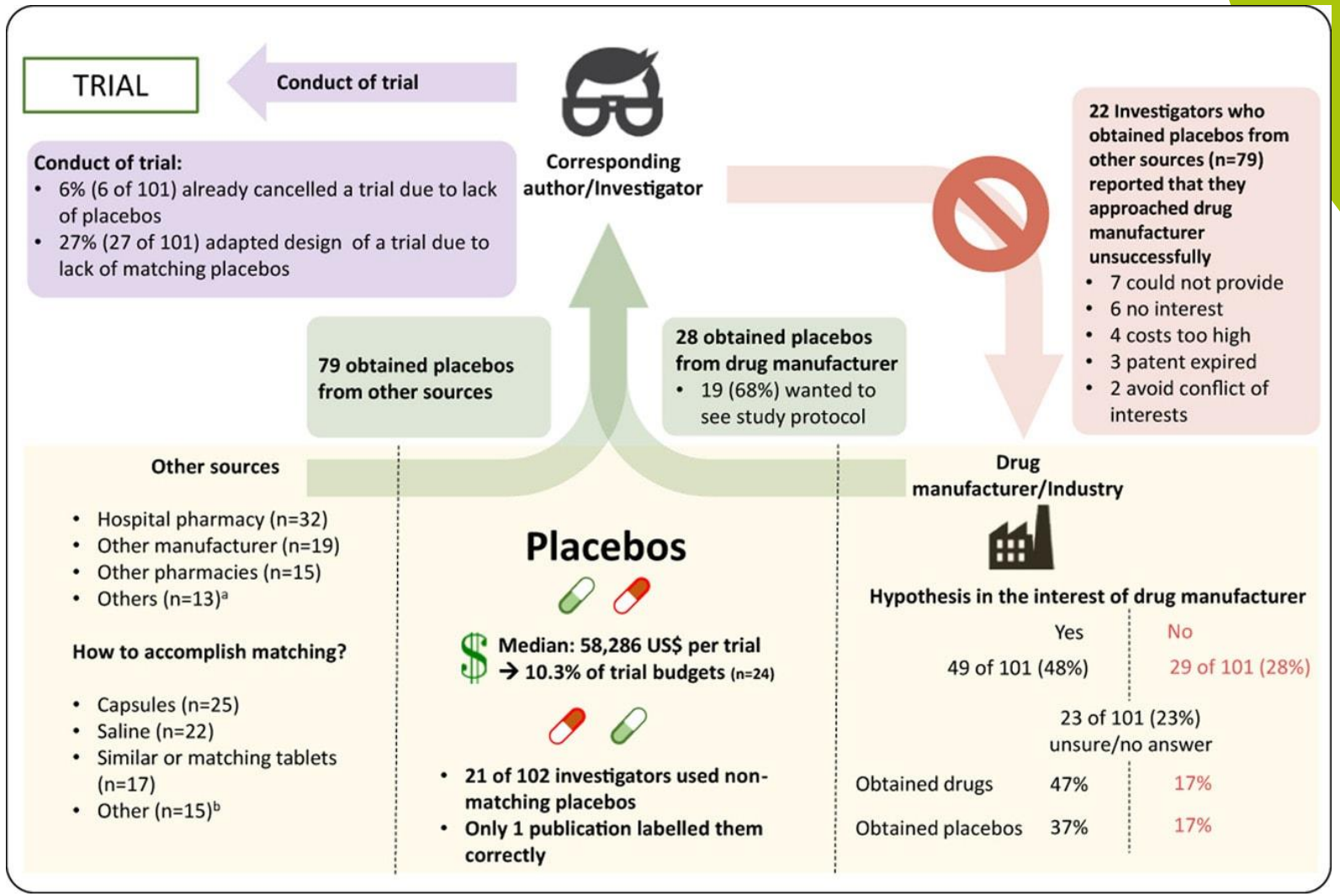


GRAPHICAL ABSTRACTS

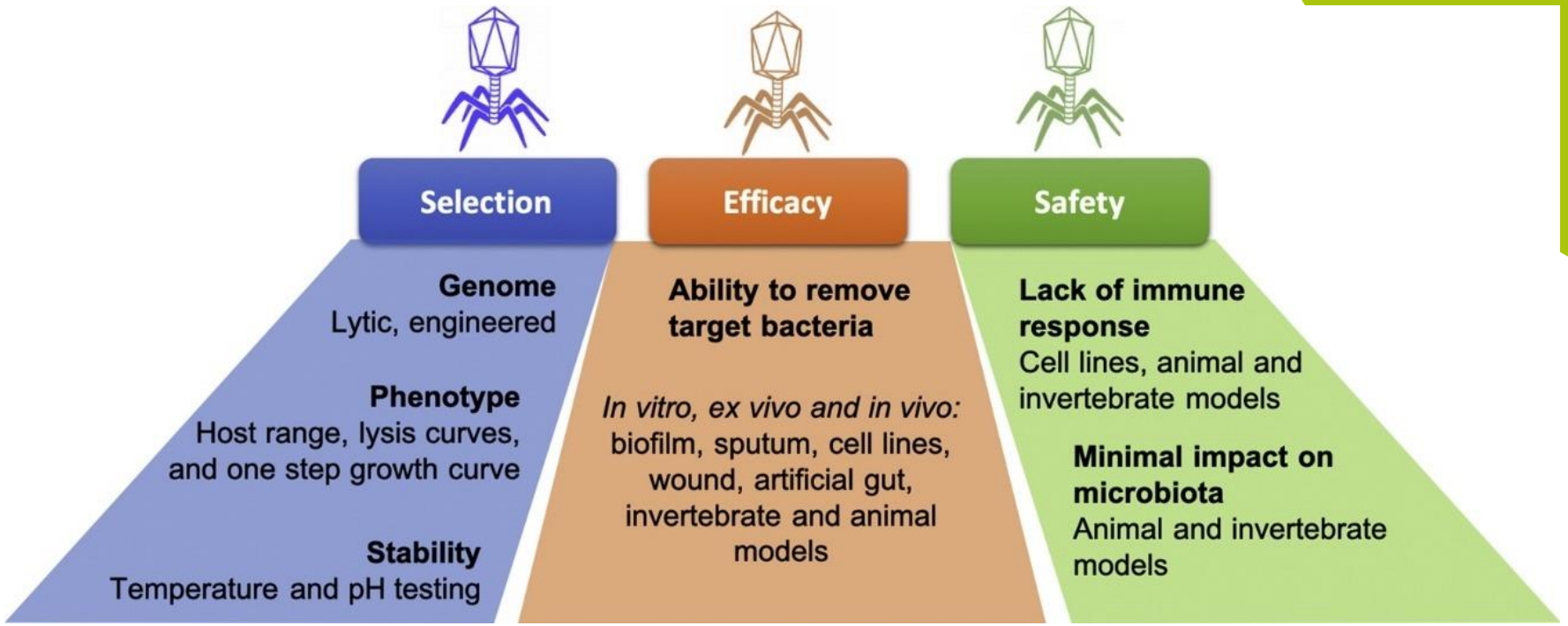




GRAPHICAL ABSTRACTS



GRAPHICAL ABSTRACTS



thx.

Skoltech