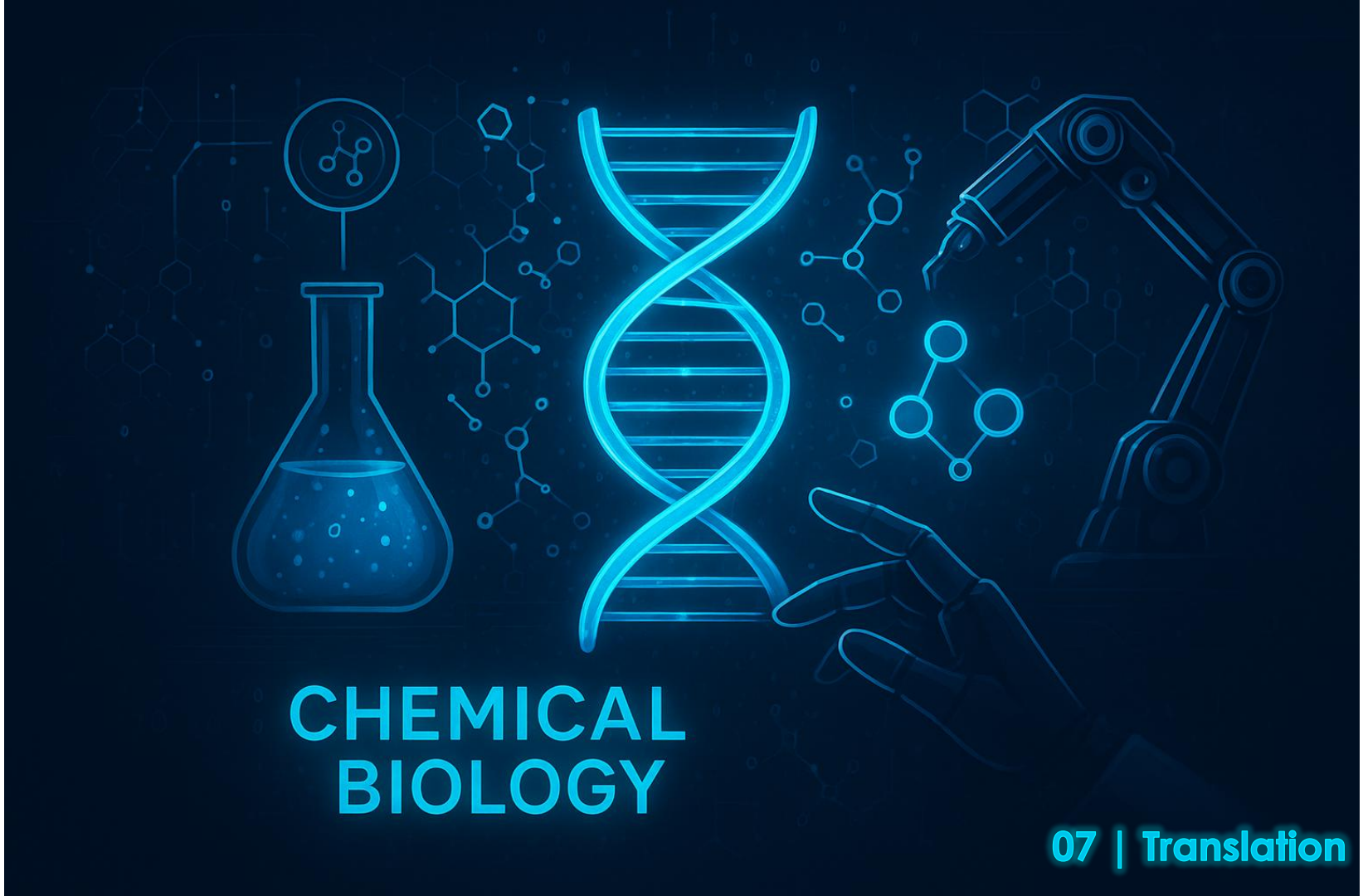

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General Course Information

- Moodle: https://go.epfl.ch/CH-313
  - Lecture slides (evening before the lecture)
  - Distributed presentation topics (assignments)
  - Forum (for questions and announcements)

- Examination (written, graded, detailed information will follow)
- Contact:
  - Moodle forum (for questions)
  - markus.jeschek@epfl.ch

- **“Concepts over details!”**
- **Interact! Ask! Discuss! Anytime!**

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Group Presentations

- Critical discussion of primary literature
- Illustrative examples for topics from the lecture

- Why?
  - Repetition of core concepts, techniques etc.
  - Presentation skills and critical discussion of research
  - Insight into current research topics

- How?
  - Two students per group
  - Assignments distributed one week before delivery of presentation (via Moodle)
  - **Send slides: markus.jeschek@epfl.ch (Mon evening before presentation)**
  - **15 min presentation (both group members should present!)** + Q&A

Tipps for Group Presentations

- Rough structure
  - Short intro on general topic
  - Main presentation according to assignment
  - Brief outlook incl. points of criticism/open questions/personal opinion as kick-starter for the discussion
- Everybody should participate in the discussion, incl. constructive(!) feedback on presentation style
- Questionnaires with different points, feedback by peers
- Typical assignment:
  - You will receive a certain topic including a related publication
  - Introduce the topic using the publication
  - present the motivation behind the research, methodology, key results (not every graph!)
  - Additional questions will be provided hinting towards central points
  - Be encouraged to look/present beyond the questions and the provided paper

Group Presentations – Schedule

#	Name1	Name2	Presentation on…	Assignment on…
1	Wininger Quentin	Jeremy	**Sep 23, 2025**	Sep 16, 2025
2	Ema	Ariane	**Sep 30, 2025**	Sep 23, 2025
3	Benjamin	Matthieu	**Oct 7, 2025**	Sep 30, 2025
4	Ivana	Ipek	**Oct 14, 2025**	Oct 7, 2025
5	Mridhula	Elodie	**Oct 28, 2025**	Oct 21, 2025
6	Abigail	Robin	**Nov 4, 2025**	Oct 28, 2025
7	Eva	Florian	**Nov 11, 2025**	Nov 4, 2025
8	Bastien	Axel	**Nov 18, 2025**	Nov 11, 2025
9	Melodie	Siolène	**Nov 25, 2025**	Nov 18, 2025
10	Nicole	Maria	**Dec 2, 2025**	Nov 25, 2025

Course Topics – Overview

- Week 1 | Introduction + DNA
- Week 2 | DNA
- Week 3 | DNA
- Week 4 | DNA
- Week 5 | DNA/RNA
- Week 6 | RNA/Translation
- **Week 7 | Translation**
- Week 8 | Enzymes (Zoom)
- Week 9 | Enzymes (Zoom)
- Week 10 | Enzymes/Metabolism (Zoom)
- Week 11 | Metabolism (Zoom)
- Week 12 | Engineering
- Week 13 | Engineering
- Week 14 | LSAM Intro + Exam Preparation

!Due to paternity leave the next lectures will be delivered via Zoom!

[tentative schedule]

Zoom Info

- Week 1 | Introduction + DNA
- Week 2 | DNA
- Week 3 | DNA
- Week 4 | DNA
- Week 5 | DNA/RNA
- Week 6 | RNA/Translation
- **Week 7 | Translation**
- **Week 8 | Enzymes (Zoom)**
- **Week 9 | Enzymes (Zoom)**
- **Week 10 | Enzymes/Metabolism (Zoom)**
- **Week 11 | Metabolism (Zoom)**
- Week 12 | Engineering
- Week 13 | Engineering
- Week 14 | LSAM Intro + Exam Preparation

!Due to paternity leave the next lectures will be delivered via Zoom!

https://epfl.zoom.us/j/68900732223

Meeting ID: 689 0073 2223

[tentative schedule]

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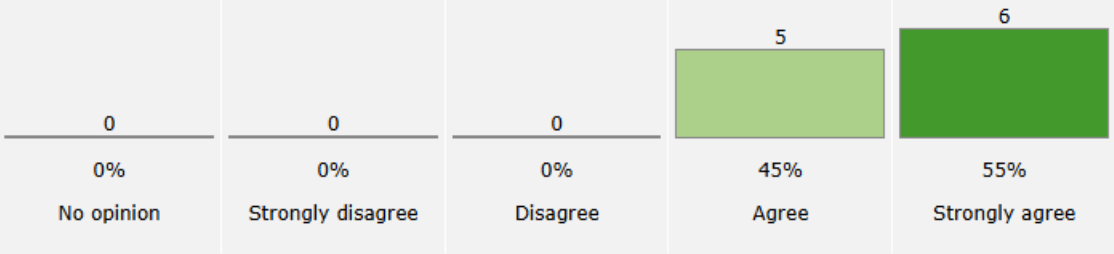
Indicative Feedback Results

Indicative Feedback – Overall Results

Year	2025-2026
Course	Chemical biology
Questionnaire	Indicative feedback of teaching (since 2022-2023)
Nb Registered	20
Nb Answered	11

The running of the course enables my learning and an appropriate class climate



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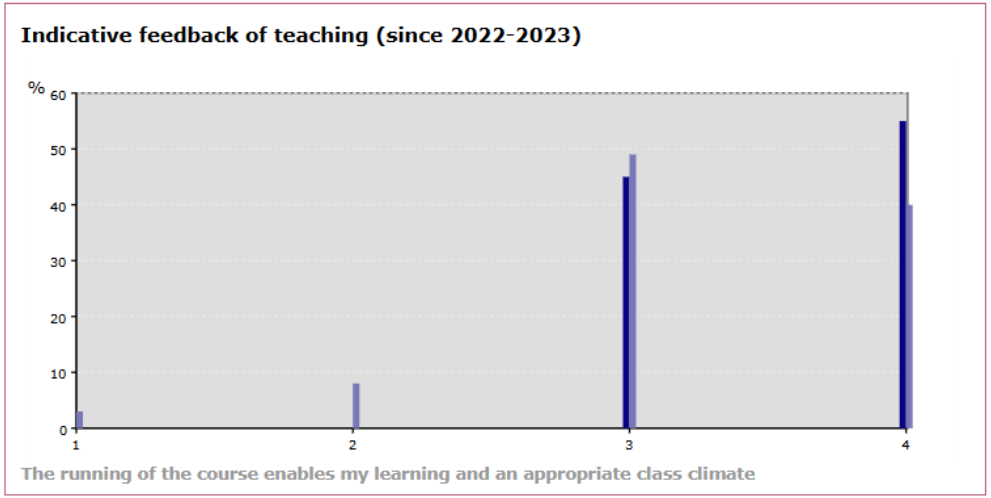
Indicative Feedback – Overall Results



Instructor(s)	Period	Semester	Section	No. registered	No. respsonses
Jeschek Markus	2025-2026	Autumn Semester		20	11
	2025-2026			-	205

Indicative Feedback – Remarks

- “Prof very nice ! I like the first part where the students present ! Class is also very interesting because it presents techniques that are currently used !”
- “The course is very interesting and the slides are very well structured.”
- “The subject matter is very interesting and gives us a good overview of the concepts of biological chemistry. The “journal club” format with a weekly presentation is also good. We are not necessarily taught how to read scientific articles critically, so I think it's a very good thing to do it here. In addition, learning to speak in front of people without the stress of being graded is beneficial. The only small point for improvement would be that exercises and/or sample questions (exam-style) would be welcome in order to see what we need to focus on and learn efficiently.”

→ **Thank you! + on exam: see next slides**

Indicative Feedback – Remarks

- “Interesting course. Some difficulties to see what kind of questions could be asked during the exam.”
- “The class is well structured and teacher explains very well but sometimes might go a bit too fast on a few new concepts but is always happy to answer to any question. To better prepare us for the exam it could be useful to show us what he expects from us and give us a few exercice sessions.
- The quantity of information is quite big and we don't know which informations are relevant for the exam. The course is therefore really well structure, the presentation is a good method to learn and the teacher is really motivating and makes the lessons really interesting.
- Some slides are a bit overcrowded, so we do not know what is really important to learn

→ Exam preparation: Example questions in last lecture (week 14!), frequent hints in the lecture, questions (“Q”) on slides

Indicative Feedback – Remarks

- “The class is well structured and teacher explains very well but sometimes might go a bit too fast on a few new concepts but is always happy to answer to any question. To better prepare us for the exam it could be useful to show us what he expects from us and give us a few exercice sessions.
- The quantity of information is quite big and we don't know which informations are relevant for the exam. The course is therefore really well structure, the presentation is a good method to learn and the teacher is really motivating and makes the lessons really interesting.
- Some slides are a bit overcrowded, so we do not know what is really important to learn

→ Speed: will be reduced, extensive slides (few!) contain all relevant information

→ Quantity: Reduced significantly compared to previous editions, focus on conceptual understanding (no learning by heart of larger lists etc.), many recaps

→ please ask/interrupt me if something is unclear/too fast!!

Protein

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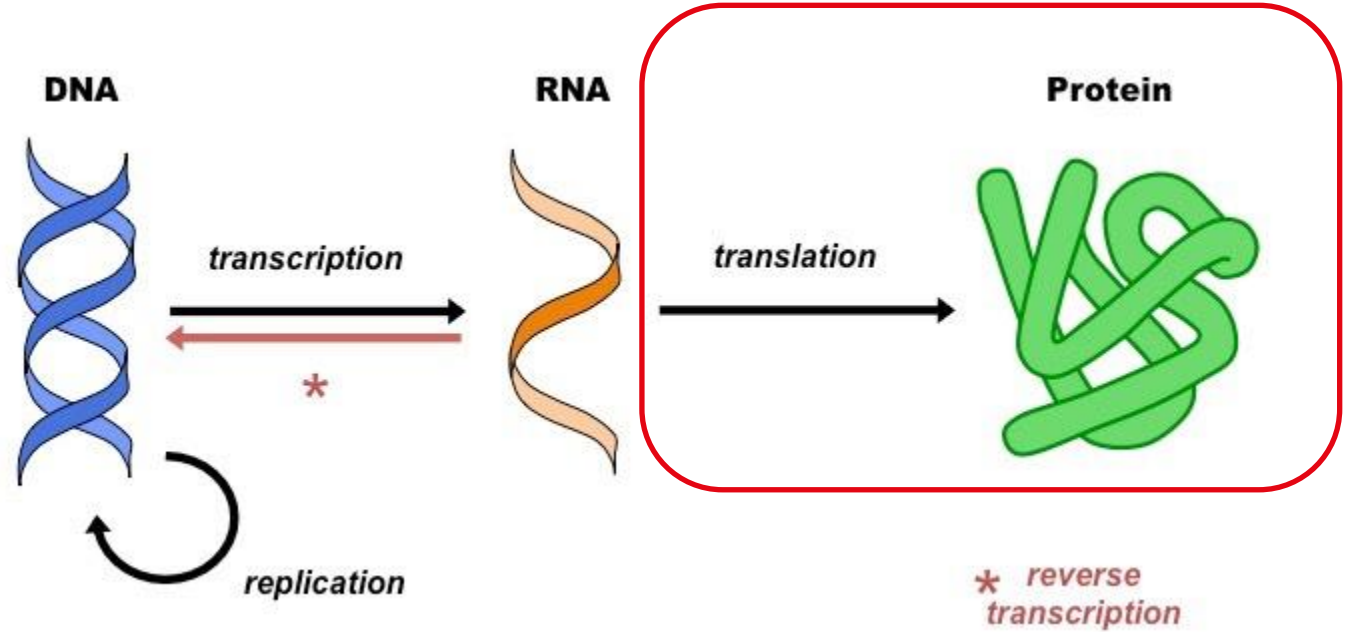
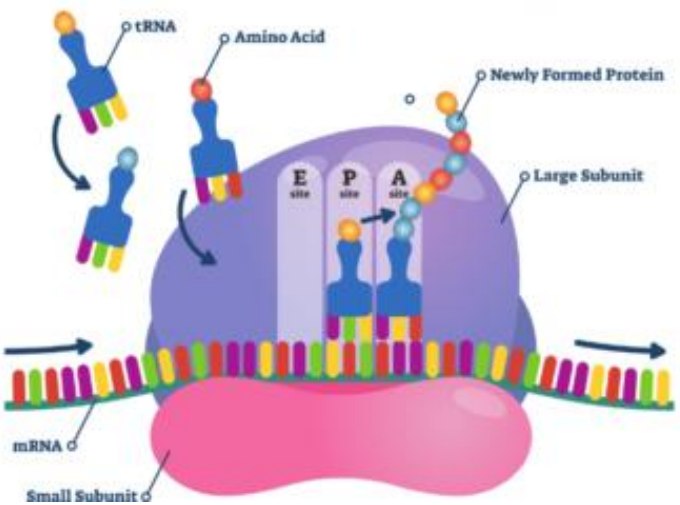
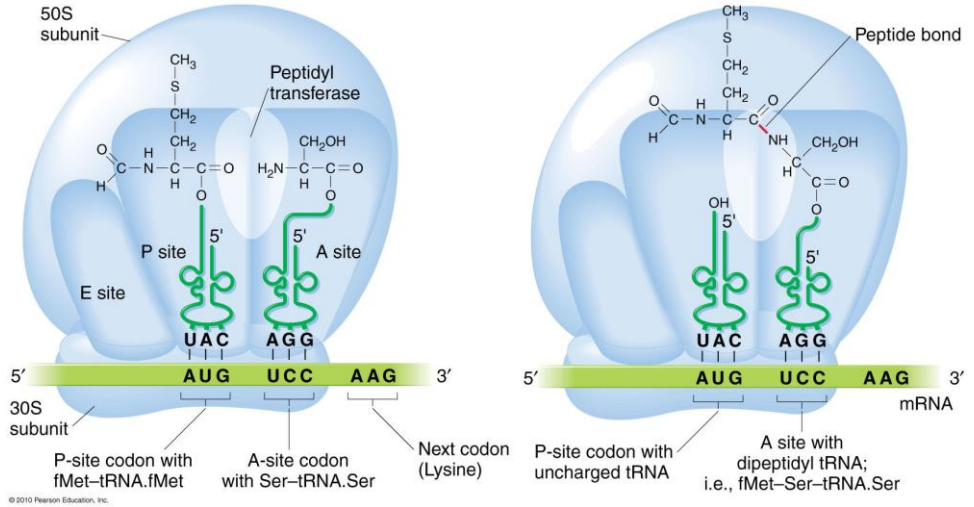
The Central Dogma

- …of Molecular Biology



Translation





- Ribosomal translation
  - approx. 10 aa/s
  - N → C direction
  - transamination (ester-amide exchange)
  - error rate approx. 10^{-4} - 10^{-3}
  - prokaryotes: in parallel with transcription
  - eukaryotes: spatial/temporal separation from transcription

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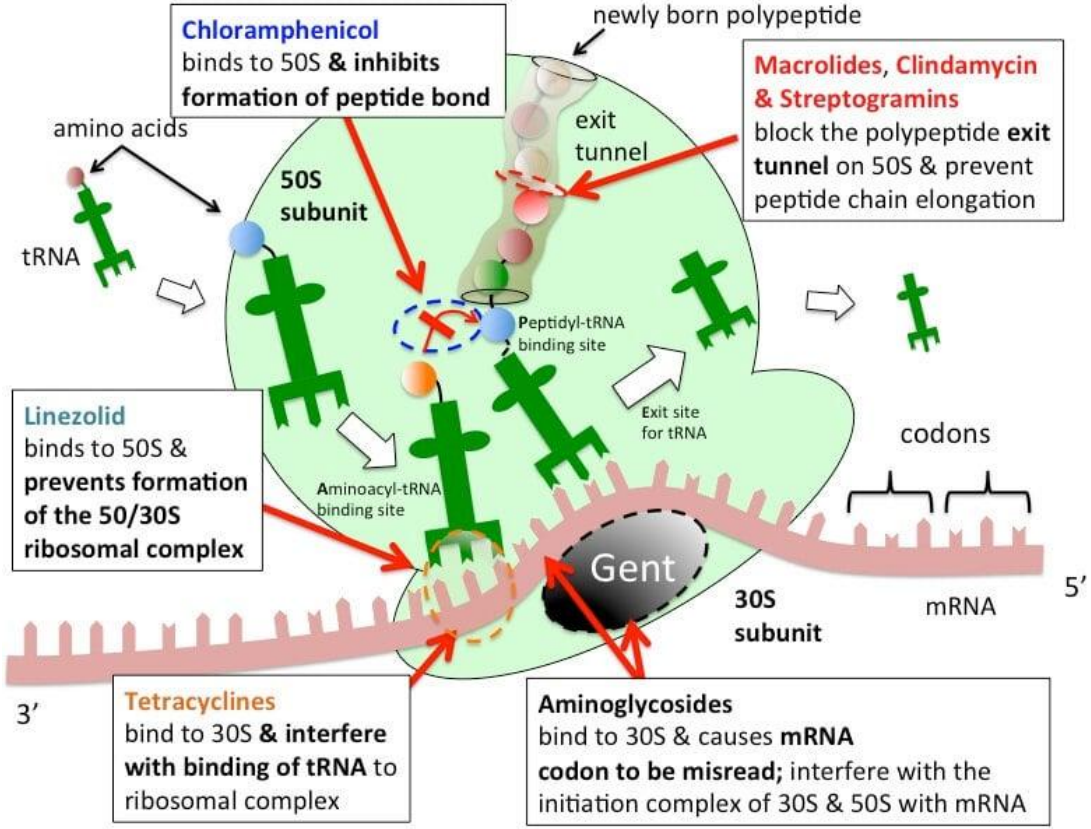
Blocking Translation – Overview



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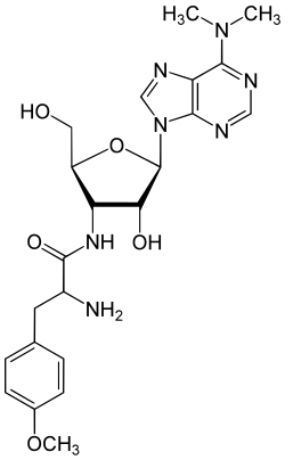
Blocking Translation – Examples

- Puromycin
  - amino nucleoside from bacteria (*Streptomyces*)
  - mimics 3'-end of loaded Tyr-tRNA
  - puromycylated chain → premature termination of translation
  - antibiotic
  - used in mRNA display



- Tetracycline
  - blocks entry of charged tRNAs to A-site
  - several species of *Streptomyces*
  - broad-spectrum antibiotic
  - specific to 30S ribosome

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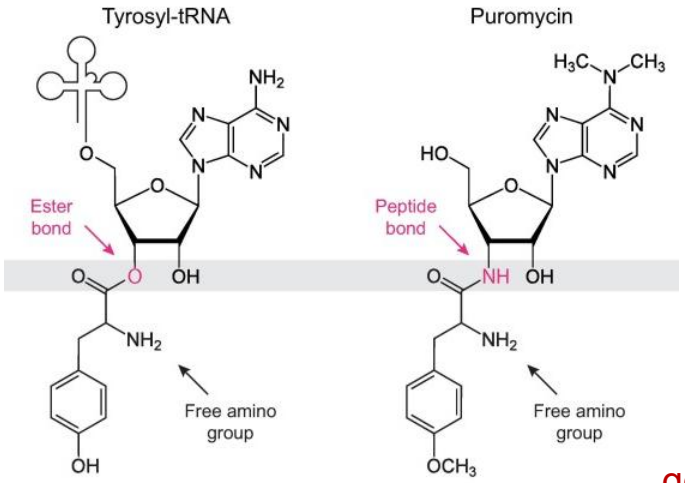
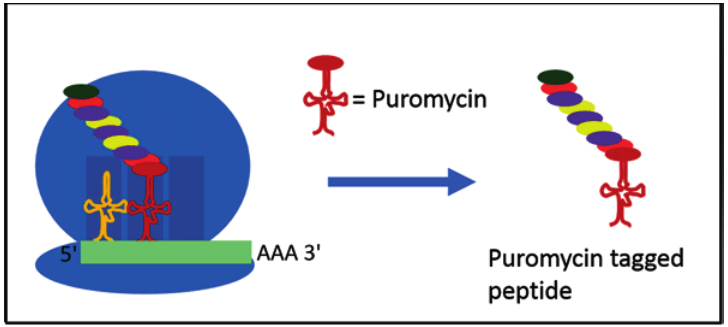
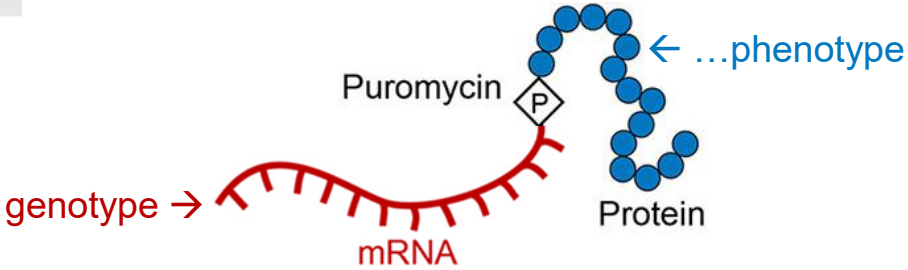
mRNA Display

- Technique for *in vitro* evolution of protein binders (up to 10^{13} variants)
- Important prerequisite: **genotype-phenotype linkage** (see “Engineering” lectures)
- Relies on puromycin







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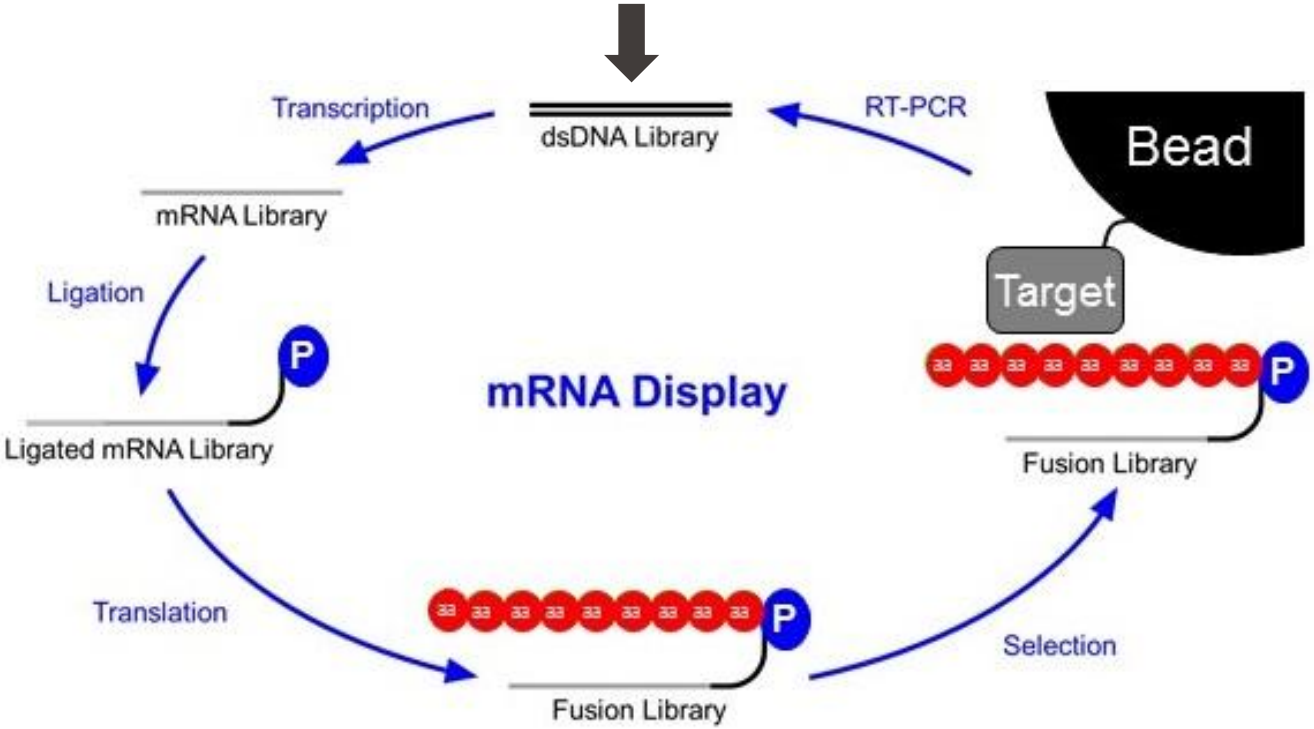
mRNA Display – Procedure

e.g. oligo synthesis,
mutagenic PCR etc.



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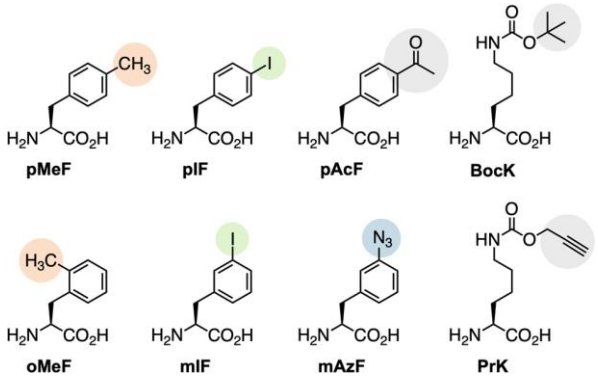
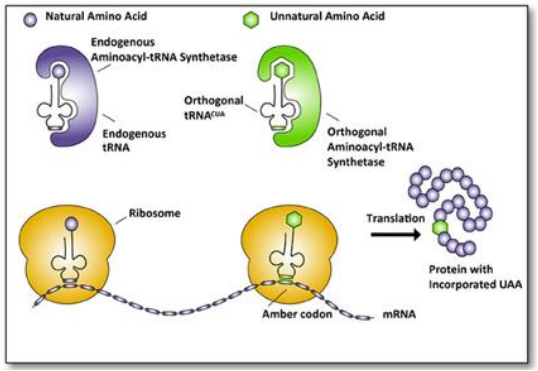
Unnatural Amino Acid Incorporation

- Incorporation of unnatural or “non-canonical” amino acids (ncAAs) into proteins

→ goal: new functionalities

- High-jacking of translation machinery
- So-called **“amber suppression” approach** (exploiting the “amber” stop codon)





In the standard genetic code, there are three different stop codons:

- In RNA:
  - UAG ("amber")
  - UAA ("ochre")
  - UGA ("opal"
- In DNA:
  - TAG ("amber")
  - TAA ("ochre")
  - TGA ("opal" or "umber")

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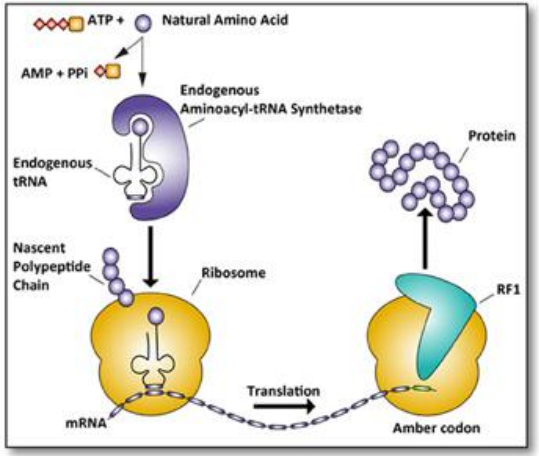
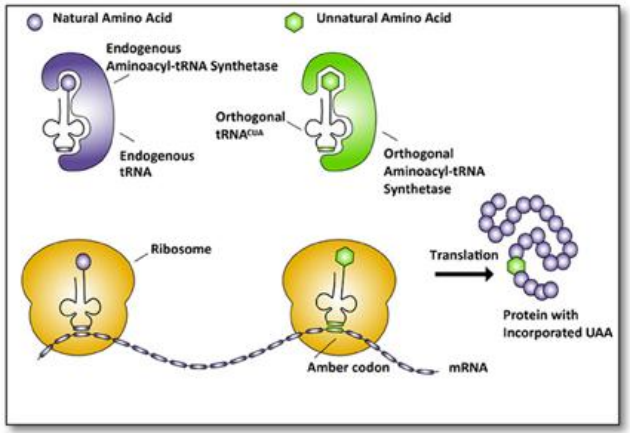
Amber Suppression – Principle

- Natural translation termination: a stop codon is decoded by a release factor (RF) aborting translation
- Amber suppression:
  - (1) a tRNA decoding the amber stop codon (UAG) is loaded with ncAA by engineered tRNA synthetase
  - (2) the ncAA is incorporated upon occurrence of UAG in the mRNA via the ribosome (instead of stopping)
- "orthogonal pair"
  - tRNA + tRNA synthetase
  - Requirements:
    - loading of tRNA with ncAA
    - no loading with other amino acids!





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Engineering Orthogonal Pairs

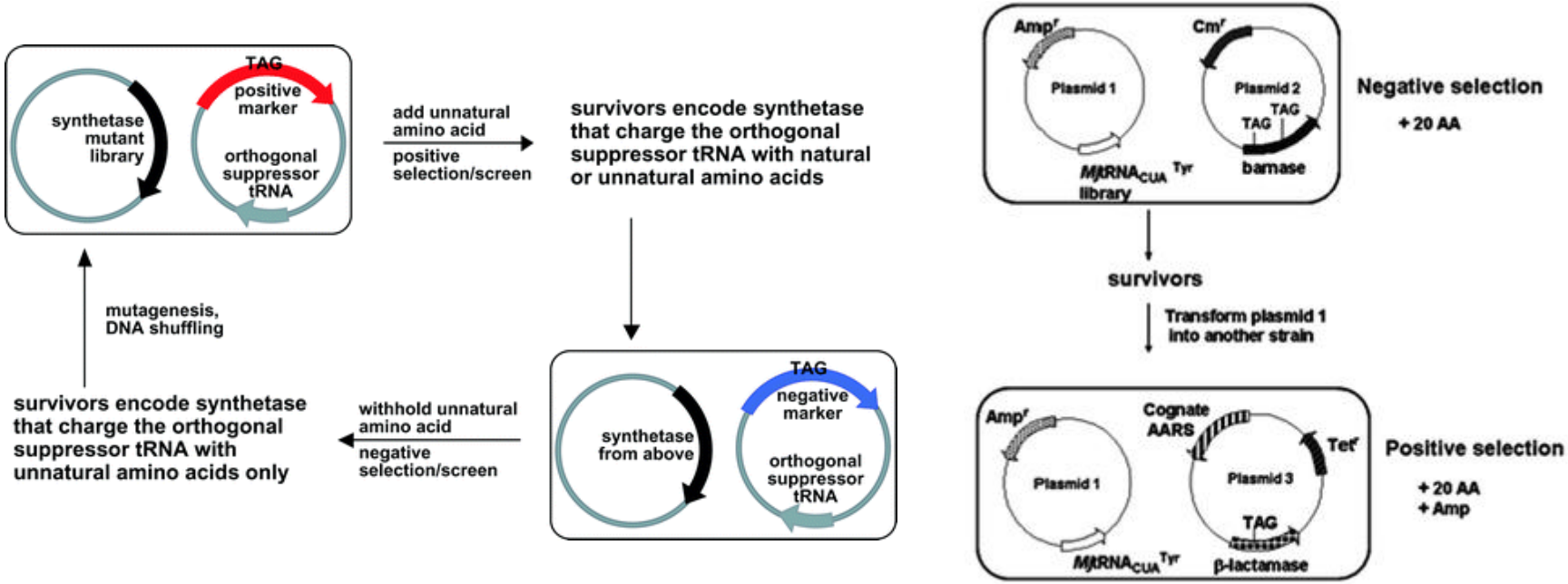
- Through iterative rounds of positive and negative selection
  - Positive selection:

  “A selectable marker gene with a TAG codon is used. Only tRNA synthetase variants that successfully incorporate an amino acid at the stop codon produce the full gene product of the marker (e.g. antibiotic resistance). Upon exposure to the ncAA and the selection pressure (e.g. antibiotic), only successful variants survive.”

  - Negative selection:

  “Surviving tRNA synthetases from the positive selection are combined with another selectable marker gene with a TAG codon. In this case, the marker (e.g. toxic gene) kills the cell if incorporation at the stop codon occurs. Here the ncAA is not added(!), leading to the depletion of unspecific synthetases”.

Engineering Orthogonal Pairs



Q: Why is the negative selection step needed?

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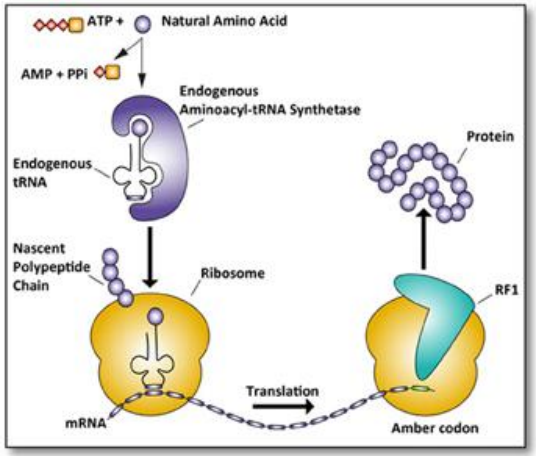
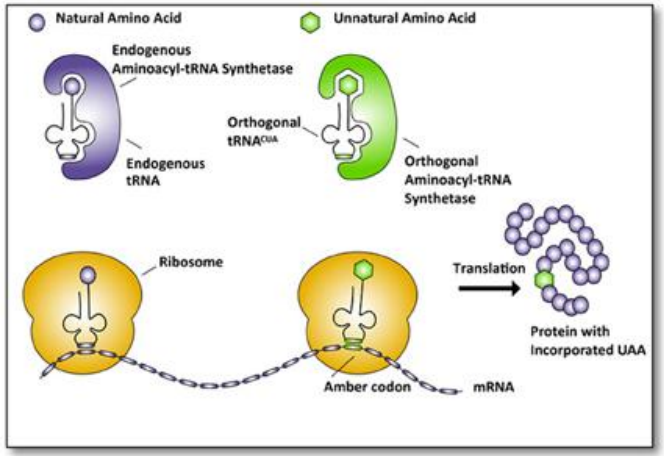
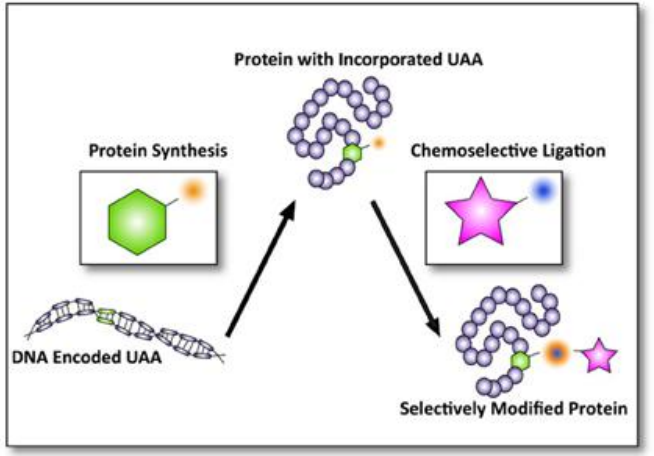
Problems of ncAA Incorporation







Q: Why could it be difficult to produce ncAA-containing proteins in natural cells (typically *E. coli*)?

Hint 1: Toxicity for cells

Hint 2: Impurity of product

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Remember?

nature

Total synthesis of *Escherichia coli* with a recoded genome

Julius Fredens[1,4], Kaihang Wang[1,2,4], Daniel de la Torre[1,4], Louise F. H. Funke[1,4], Wesley E. Robertson[1,4], Yonka Christova[1], Tiongsun Chia[1], Wolfgang H. Schmied[1], Daniel L. Dunkelmann[1], Václav Beránek[1], Chayasith Uttamapinant[1,3] Andres Gonzalez Llamazares[1], Thomas S. Elliott[1] & Jason W. Chin[1]*

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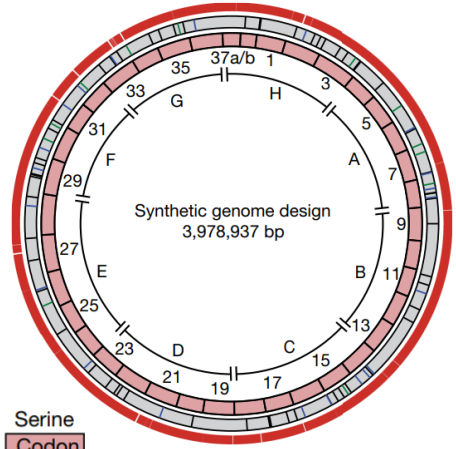
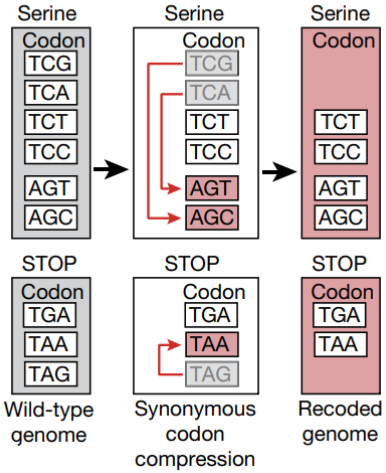


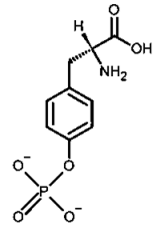


Unnatural Amino Acid Incorporation

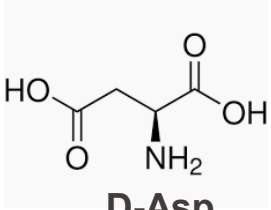
- Incorporation of hundreds of non-canonical amino acids (ncAAs) demonstrated

→ goal: new functionalities

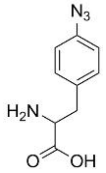
- Examples:
  - Post-translational modifications
  - D-amino acids, beta-amino acids
  - Reactive chemical “handles” (azides, alkynes etc.)



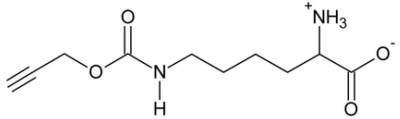
phosphotyrosine



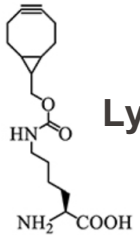
D-Asp



pAzF



N-propargyloxy-carbonyl-L-lysine



Lys-derivative for SPAAC

Q: What could these examples be used for?

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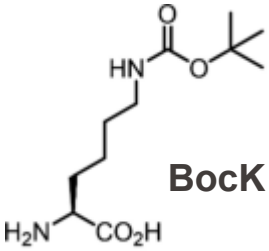
Unnatural Amino Acid Incorporation

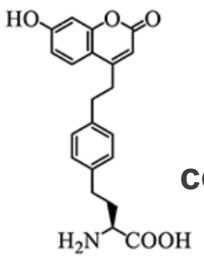
- Incorporation of hundreds of non-canonical amino acids (ncAAs) demonstrated

→ goal: new functionalities

- Examples:
  - Post-translational modifications (pure production/testing!)
  - D-amino acids, beta-amino acids
  - Reactive chemical “handles” (azides, alkynes etc.)
  - Blocked amino acids
  - Fluorescent amino acids
  - Photo-caged/-switchable amino acids

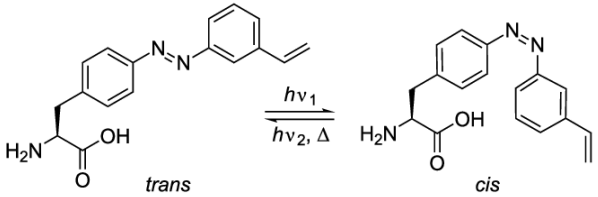


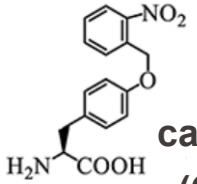
BocK



coumarinylated Phe

azobenzene amino acids





caged Tyr (ONBY)

Q: What could these examples be used for?

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