

First name:

Family name:

Written Exam

Methods in Drug Development (CH-455)

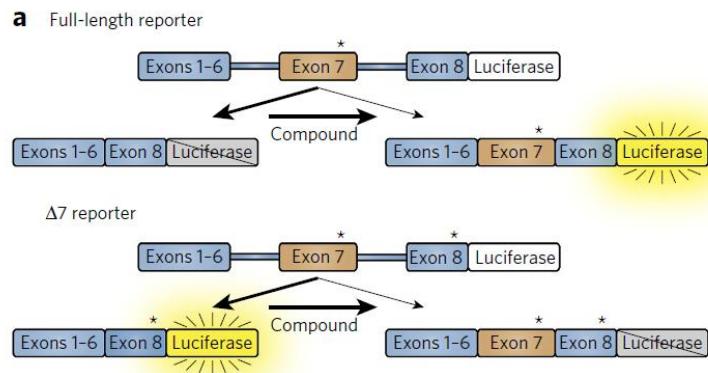
Example Exam

Prof. Christian Heinis

- Exam duration: 2 hours
- For students who have been granted an extension by the SA: 50 minutes (170 minutes in total)
- Please check that you have 8 questions.
- One point can be awarded for each question (8 points in total).
- Place your student ID on the table (we will check your identity during the exam).
- Allowed material: pencil, pen (no books, no notes, no calculator, etc.).
- Write your name on each page.
- In order to treat all students equally, we will not answer comprehension questions.
- Please ask if you would like to go to the restroom.
- When you are finished with the exam, please hand in your copy to the teachers near the blackboard and sign your name on a sheet provided.
- If you finish early, please return your copy earlier and leave the room in silence.

Question 1: Phenotypic screening

The following assay principles were used for high-throughput screening and to identify a small molecule that can correct splicing.



(a) Please add a cross to indicate if the following statements are correct or wrong:

	Correct	Wrong
Introns are coding regions.	<input type="checkbox"/>	<input type="checkbox"/>
Exons are coding regions.	<input type="checkbox"/>	<input type="checkbox"/>
Splicing happens with the translated protein.	<input type="checkbox"/>	<input type="checkbox"/>
Splicing happens with the mRNA.	<input type="checkbox"/>	<input type="checkbox"/>

(b) Please add a cross to indicate if the following statements are correct or wrong:

	Correct	Wrong
A screening hit leads to increased luciferase activity in the full-length reporter assay	<input type="checkbox"/>	<input type="checkbox"/>
If a compound of the library inhibits luciferase, it would appear as a false positive hit in the $\Delta 7$ reporter assay.	<input type="checkbox"/>	<input type="checkbox"/>
Around 10,000 small molecules were screened with the two assays.	<input type="checkbox"/>	<input type="checkbox"/>
The $\Delta 7$ reporter assay represents the disease situation (in-frame splicing in absence of compound).	<input type="checkbox"/>	<input type="checkbox"/>

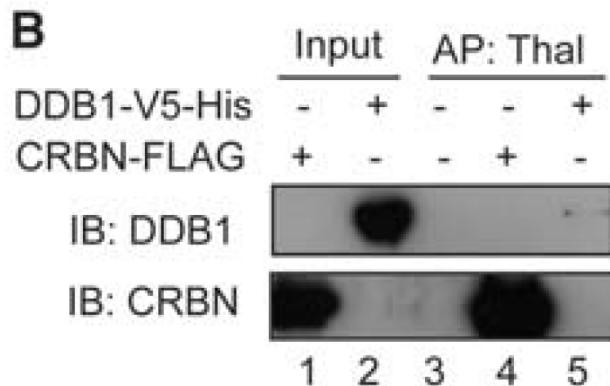
(c) Why is Exon 7 not efficiently included in SMN2 (molecular basis)?

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Question 2: Target identification

The following experimental result was obtained when searching the target of the teratogenic compound thalidomide.



(a) Please add a cross to indicate if the following statements are correct or wrong:

	Correct	Wrong
The image shows a Coomassie-stained protein gel.	<input type="checkbox"/>	<input type="checkbox"/>
The image shows a Western blot.	<input type="checkbox"/>	<input type="checkbox"/>
The lanes "input" were applied to test the binding of DDB1 and CRBN.	<input type="checkbox"/>	<input type="checkbox"/>
Three of the proteins bind to thalidomide	<input type="checkbox"/>	<input type="checkbox"/>

(b) Please indicate the meaning of the following labels with one keyword each.

"label"	Keyword
IB	
AP	
His, FLAG	
Input	

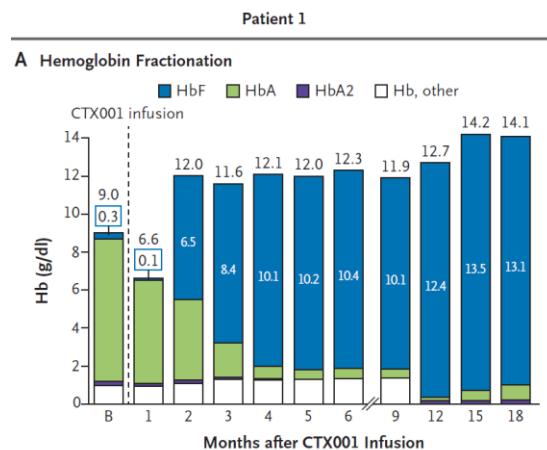
(c) Which protein is binding to thalidomide in this assay?

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Question 3: CRISPR Cas9

A new approach based on CRISPR-Cas9 was applied to edit a gene in a patient with β -thalassemia.



(a) Please add a cross to indicate if the following statements are correct or wrong:

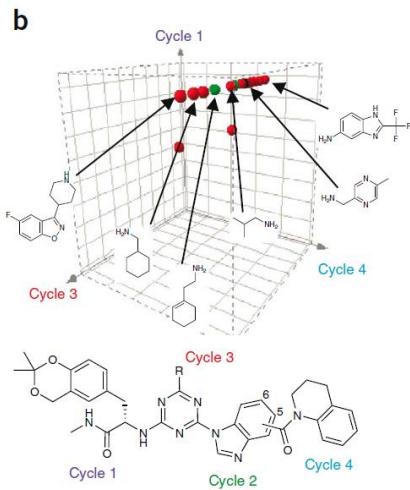
	Correct	Wrong
The aim of the gene editing was to increase expression of fetal hemoglobin.	<input type="checkbox"/>	<input type="checkbox"/>
CRISPR-Cas9 was applied to correct a frameshift mutation.	<input type="checkbox"/>	<input type="checkbox"/>
The guide RNA was introduced by a viral vector.	<input type="checkbox"/>	<input type="checkbox"/>
The therapy was applied in this study to around 100 patients.	<input type="checkbox"/>	<input type="checkbox"/>

(b) Please answer the following questions by a single keyword.

Question	Keyword
What is "HbF"	
Is "CTX001" a DNA, an RNA, a cell or a protein?	
Which Hb is better for this patient HbA or HbF?	
How much HbF did this patient have before the treatment?	

Question 4: DNA encoded libraries

DNA-encoded libraries are now broadly used in pharmaceutical companies for small molecule ligand identification.



(a) Please add a cross to indicate if the following statements are correct or wrong:

	Correct	Wrong
The DNA-encoded libraries discussed contain more than a million different compounds.	<input type="checkbox"/>	<input type="checkbox"/>
The DNA tags is a single-stranded DNA.	<input type="checkbox"/>	<input type="checkbox"/>
Each different DNA-encoded molecule occurs in around hundred copies in the library.	<input type="checkbox"/>	<input type="checkbox"/>
After the affinity selections, more than hundred-thousand of DNA codes are sequenced.	<input type="checkbox"/>	<input type="checkbox"/>

(b) Please answer the following questions about the above 3D-map:

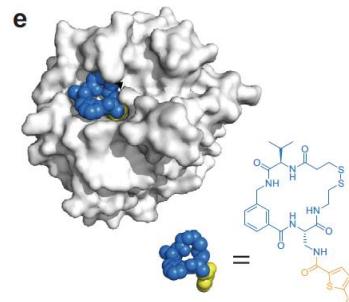
Question	Keyword
Which two building blocks are most important in the above isolated compounds (e.g. cycle 1, 2, 3, 4)?	
Which chemical group was kept constant in all compounds shown in the graph?	
To which building block was the DNA linked (e.g. cycle 1, 2, 3, 4)?	

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Question 5: Combinatorial libraries and macrocycles

Macrocycles are an attractive class of molecules for drug development due to their good binding properties and their ability to cross membranes.



(a) The macrocycle shown above inhibits thrombin and was obtained by synthesizing and screening a large library. Please describe the chemical reaction(s) that was/were used to generate the compounds in the library.

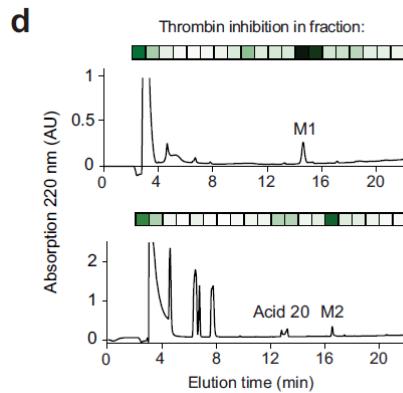
(b) In which volumes were the macrocycle compounds synthesized and how were the reagents transferred?

(c) What was the aim of the experiment shown in the figure?

d

Thrombin inhibition in fraction:

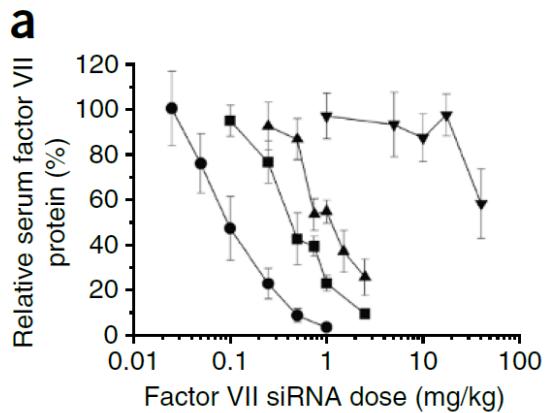




Question 6: Lipid nanoparticles (LNPs) and RNA therapeutics

LNPs are used to deliver RNA-based therapeutics into cells.

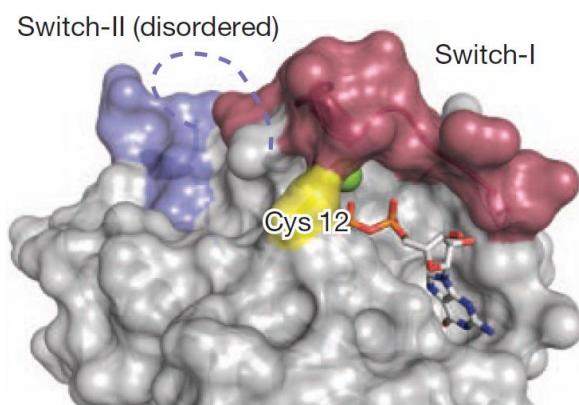
(a) The graph shows the performance of LNPs that are based on four different cationic lipids. Which one of the lipids performed best (indicate the symbol)?



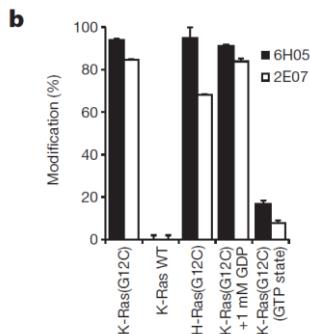
(b) What was the rational to test cationic (positively charged) lipids?

Question 7: Covalent drugs

(a) Please describe the general format/structure of molecules that were tested for covalently inhibiting K-Ras G12C and show the chemical reaction.

a

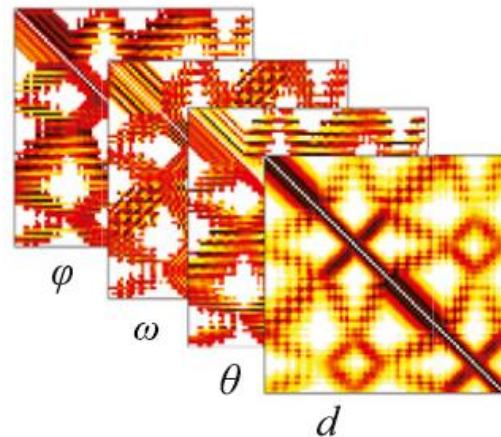
(b) Why did the inhibitors 6H05 and 2E07 not inhibit wild-type K-Ras?



Question 8: Protein structure prediction

Enormous advances were recently made in computationally predicting the 3-dimensional structures of proteins.

(a) What is shown on the x- and y-axes of these four graphs? Please propose how you would label the axes.



(b) Please describe in one sentence the meaning of “ $\varphi \omega \theta$ ”

(c) Please describe in one sentence the meaning of “ d ”.