BIO-467: SCIENTIFIC LITERATURE ANALYSIS IN BIOENGINEERING (INM 203)

Summary:

Search and utilize effectively scientific literature in the multidisciplinary field of bioengineering including bioinstrumentation at the nano- and micro-scale, cellular and molecular engineering, quantitative biology and analytics.

Learning outcomes:

- Analyze scientific papers in a selection of bioengineering fields
- Interpret the results reported in the scientific literature
- Compare results with claims
- Compare among different papers the respective approaches chosen to a similar aim
- Synthesize the main messages of a scientific work
- Differentiate review and original works and other paper types

Transversal skills

- Work in a team
- Demonstrate the capacity for critical thinking
- Summarize an article or a technical report
- Make an oral presentation
- Write a literature review which assesses the state of the art
- Access and evaluate appropriate sources of information
- Provide critical and constructive feedback

Wed 8h15-10h00 (Default time unless otherwise noted) / classroom: INM 203

Schedule and course organization

BIO 467 Fall 2024

#	DATE		TOPIC	WHO
1	Sept	11	General Introduction **(all students join)**	**Aleks Antanasijevic**
2	Sept	18	Librarian lecture on scientific literature search Intro Module 1 (**all students join starting at 10:00 am-Christoph)**	**EPFL Library Team**
			Module 1	
3	Sep	25	Groups ABC DEF will be assigned on Monday of the week Prep Module 1 (TA's available in classroom)	**Christoph Merten**
4	Oct	02	Module 1 group **ABC** only	
5	Oct	09	Module 1 group **DEF** only Introduce Module 2 (**all students join starting at 10am-Aleks**)	
			Module 2	
6	Oct	16	Prep Module 2 (TA's available in classroom)	**Aleks Antanasijevic**
	Oct	23	**Holidays!**	
7	Oct	30	Module 2 group **DEF** only	
8	Nov	6	Module 2 group **ABC** only Intro Module 3 and Intro individual topics (**all students join starting at 10am-Hatice**)	
			Module 3	
9	Nov	13	Prep Module 3 (TA's available in classroom)	**Hatice Altug**
10	Nov	20	Module 3 group **ABC** only	
11	Nov	27	Module 3 group **DEF** only	
			Individual efforts	
12	Dec	4	Preparation for individual report and presentation	**ALL**
13	Dec	11	Preparation for individual report and presentation	
14	Dec	18	Hand in reports (due 23:59 Dec 17th); **8.15am - noon** Individual presentations (**all students**)	

Introducing Professors

- Christoph Merten (MED 1 2815) – Module 1
  - Laboratory of Biomedical Microfluidics
  - Lab website: https://www.epfl.ch/labs/lbmm/
  - Email: christoph.merten@epfl.ch

- Aleksandar Antanasijevic (SV 3531) – Module 2
  - Laboratory of Virology and Structural Immunology
  - Lab website: www.epfl.ch/labs/antanasijevic-lab/
  - Email: aleksandar.antanasijevic@epfl.ch

- Hatice Altug (BM 4133) – Module 3
  - Laboratory of BIOnanophotonic Systems (BIOS)
  - Lab website: https://www.epfl.ch/labs/bios/
  - Email: hatice.altug@epfl.ch

Introducing TAs

- Christoph Merten
  - Remo Bättig (remo.battig@epfl.ch)
  - Roger Diaz Codina (roger.diazcodina@epfl.ch)
- Aleksandar Antanasijevic
  - Yash Garodia (yash.garodia@epfl.ch)
  - Kiruthika Kumar (kiruthika.kumar@epfl.ch)
- Hatice Altug
  - Jiayi Tan (jiayi.tan@epfl.ch)
  - Berkay Dagli (berkay.dagli@epfl.ch)

Location

BIO-467 will be given in person (all lectures and exercises in **INM 203**).

No zoom link or recorded video will be provided.

Office hours with the teachers

Course time in the preparation weeks (Sep 25th, Oct 16th, Nov 13th)

- or upon appointment by email (please contact the respective Prof in advance)

Moodle

All the logistic documents including lecture notes, relevant papers, etc will be uploaded on Moodle

https://moodle.epfl.ch/course/view.php?id=14856

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Module 1, 2 and 3 (group efforts)
read & analyze scientific papers to understand a chosen topic (determined by the teacher) and present to the class

As an example, let's take a look at module 1's organization (Christoph Merten)

Sep 18 (at the end of the lecture time)
A brief introduction to the topic. The selected papers (1-3/group) will be given this week.

Sep 25 (flexible time/place)
Preparation for Module 1. You can get support from the TAs in the classroom during course time. You can also contact them to schedule a different time.

Oct 02 (Group A, B, C only)
Module 1 presentation: presentation of the assigned papers, evaluate other groups' presentations

Oct 09 (Group D, E, F only)
Module 1 presentation: presentation of the assigned papers, evaluate other groups' presentations

Teaching method – Group effort

Time allocated:
Wednesdays 8:15am – 10am

The class will be split into groups of 3 or 4 students: A, B, C and D, E, F.

For each module:

- Each group will be assigned a set of papers (1-3 papers usually) one week ahead of the prep week.
- You have at least two weeks to prepare.
- You are expected to carry on additional literature search for critical assessment of the papers, develop deeper understanding of the field, application, scientific questions addressed by the papers.
- Collaborate with your group to discuss your findings & understandings.
- TAs can help to analyze the papers, answer questions (during course time of prep week; plus anywhere/anytime, upon the agreement between TAs and the students) during the prep week.
- Each group will present their papers (20' presentation + 10' Q&A): ALL students in the group present
- Evaluate the presentations by other groups, send your group evaluation to the professor within the same week (one evaluation form for each evaluated group, summarizing all group members' opinions)
- ONLY the groups presenting (e.g, ABC) need to be there; the other groups (e.g, DEF) prepare for their presentations
- After all the presentations, the Prof. of the module will summarize all the feedback (his/her own, TAs', students') and give the group an overall feedback

Evaluation form for Module 1, 2 & 3 (group efforts)

Evaluation/feedback received for each presentation:

Example: **Module 1 – Group A presents**

Feedbacks to be collected from:

- Group B
- Group C
- TAs (1-3)
- Teacher of the respective module

The teacher will collect/summarize all and give an overall feedback to the group (by email)

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Grading report

Group to be evaluated: Evaluation by (Group, TA, or Prof.):

Module #: Prof.
Date:

Depth of understanding of the papers' content
Level of understanding of the scientific field of the set of papers supported by additional literature search:
Quality of the presentation (slides):
Quality of the presentation (oral):
Critical analysis, discussion and comparison of the presented set of papers:
Quality of the answers given in response to the audience questions:
Additional optional comments:

Individual efforts

Each individual student will be assigned a specific topic, on which he/she submits a written report and gives a short presentation of the topic with papers of his/her own choice.

Sep 18
Librarian lecture on scientific literature search: learn how to use the scientific databases, reference managing software, and how to perform a literature search of a given topic **(a survey needed the week before by email)**

Nov 6
Assign individual topics: the topics are relevant to the fields studied in Module 1-3; each student will be assigned a topic randomly

Dec 4 and 11
Preparation weeks: TAs can provide input upon appointment

Dec 17, 23:59 Individual written report is due (upload to Moodle)

Dec 18 (8:15h-12h; divided into 2 sessions: 1st session – topic 1-10; 2nd session – topic 11-21)
Individual presentation: presentation of the assigned topic with individually searched and selected papers

Teaching method – Individual effort

- Literature search: individual literature search on a topic chosen by you from one of the proposed areas/topics by teachers.
- Narrow down the topic if necessary
- Carry on thorough literature search within the topic using various tools
- Summarize the literature you found (use figures if necessary)
- Understand what are the remaining challenges and future directions in the field
- **TAs** can provide some input or answer questions upon appointment
- Understand the topic and **present the state of the art to the class** (**7' presentation + 3' Q&A**)
- Active participation in Q&A by the listening students is encouraged

Teaching method – Individual effort (cont')

- **Written report**: **no more than 3 pages, at least 11 font size, use template**
- Hand in the report (**upload to Moodle - TBA**) the day before individual presentations (**due Dec 17, 23:59**)

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Individual Literature Search Report (no more than 3 pages)

Name of the student: Topic:

....

Briefly summarize the state of the art of the field you chose:
List some of the major publications, groups working on the topic, and demonstrations:
Indicate timeline and statistics on the publication volume (you could include figures):
Based on your scientific literature search, what are the future directions that you foresee and/or the most important open questions?

Assessment method

- 60% average of performance at 3 module presentations
- 25% evaluation of report and presentation on individual literature search
- 15% feedback and discussion on the other’s presentations

Groups will be formed at the end of next week by the teachers, but if you find somebody to swap with, that’s fine!

Some basics about scientific literature

- Why do we publish papers in academia?
- Different types of papers

  Conference papers
  Journal papers: original (letters, articles), review papers (review, insight, perspective, “book chapters” …)
  Preprints (most recent, but NOT yet peer-reviewed)
- What is the process of publishing papers (what is a peer-review process?)
- List some major journals in bioengineering
- How to undertake a literature search?

Content of a scientific paper

- Title
- Authors & affiliations
- Abstract
- Main Body
  - Introduction & motivation
  - Materials & Methods
  - Results
  - Discussion
  - Conclusion
  - Reference
- Figures & Tables (figure captions)

Analytical approaches

- Critical analysis of claims and data
- Review process
- Comparison of papers in the same field
- Analysis of the development in time of a research project

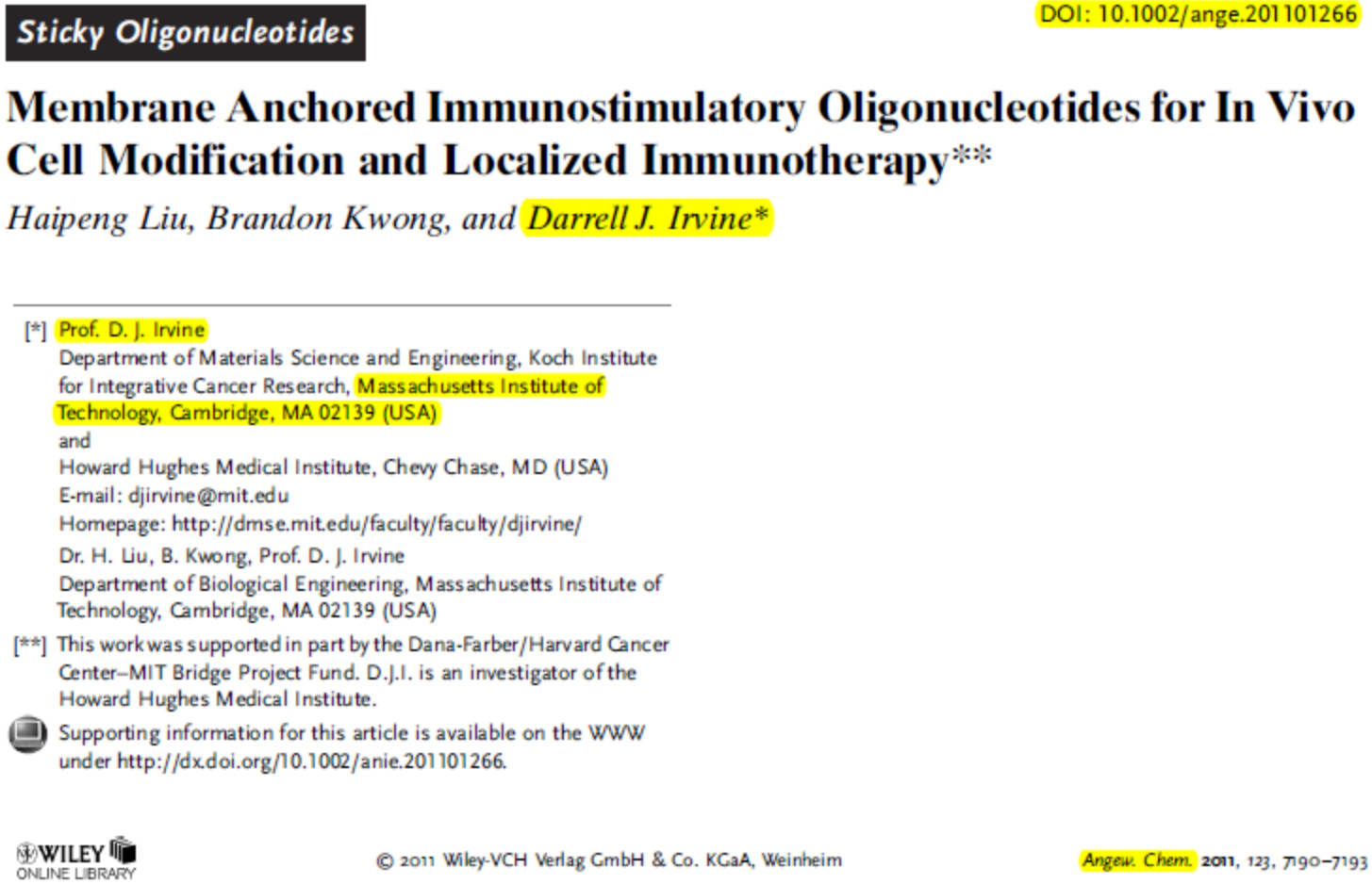
How to start when you read a paper?

…a case study by Li Tang

(with further inputs from Chan Cao, Christoph Merten and Aleks Antanasijevic)

Take the following questions with you when you start to read a paper:

basic information



Sticky Oligonucleotides

DOI: 10.1002/ange.201101266

Membrane Anchored Immunostimulatory Oligonucleotides for In Vivo Cell Modification and Localized Immunotherapy**

*Haipeng Liu, Brandon Kwong, and Darrell J. Irvine**

[*] Prof. D. J. Irvine
Department of Materials Science and Engineering, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139 (USA)
and
Howard Hughes Medical Institute, Chevy Chase, MD (USA)
E-mail: djirvine@mit.edu
Homepage: http://dmse.mit.edu/faculty/faculty/djirvine/
Dr. H. Liu, B. Kwong, Prof. D. J. Irvine
Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139 (USA)

[**] This work was supported in part by the Dana-Farber/Harvard Cancer Center–MIT Bridge Project Fund. D.J.I. is an investigator of the Howard Hughes Medical Institute.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201101266.

Angewandte Chemie (meaning "Applied Chemistry") is a weekly peer-reviewed scientific journal that is published by Wiley-VCH on behalf of the German Chemical Society(Gesellschaft Deutscher Chemiker). Its current impact factor is 16.6 (2023).

From wiki: https://en.wikipedia.org/wiki/Angewandte_Chemie

position the paper

Locally delivered immunomodulators are utilized to treat unresectable tumors and solid tumor resection sites to prevent local recurrence.[1] Synthetic immunostimulatory oligonucleotides such as double-stranded RNA or unmethylated cytosine–guanosine motifs (CpG-ODNs) mimic molecular signatures of pathogens (viruses or bacteria, respectively) and trigger an immunostimulatory cascade including maturation, differentiation and proliferation of multiple host immune cells through pattern recognition receptors.[2] As a result, these synthetic ODNs have been extensively studied as therapeutic agents for cancer and as vaccine adjuvants.[2] However, a key element for the effectiveness of immunostimulatory ODNs is the close association of oligonucleotides with tumor antigen or tumor cells. For example, intratumoral/peritumoral CpG-ODN injections can lead to tumor regression in settings where intravenous CpG treatment has no effect.[3] Also to this end, several CpG adjuvant studies indicated that co-delivery of CpG and antigens to the same antigen presenting cells (APC) significantly enhances antitumor responses.[4] Two fundamental limitations of directly injecting ODNs into tumors are 1) relatively rapid loss of ODNs from the injection site due to their relatively low molecular weights and 2) lack of physical association between tumor cells and ODNs. We hypothesized that a membrane-interactive ODN that could spontaneously insert into cell membranes would in principle overcome both of these limitations, by prolonging ODN retention at tumor sites and more importantly, by providing a physical connection between tumor cells and ODNs.

What's the field:

Locally delivered immunomodulators

↓

Synthetic immunostimulatory oligonucleotides

Keywords: cancer · cell surface modification · immunotherapy · in vivo techniques · oligonucleotides

What's the challenge in the field:

Current solutions:

Current limitations:

What's new here:

key argument(s)/technology(ies)

In summary, we have demonstrated a facile and simple method for in vivo cell modification with single-stranded or double-stranded immunostimulatory oligonucleotides. Local injection of membrane anchored ODN not only promoted an in situ membrane insertion, resulting in a higher local concentration of ODN within the tumor microenvironment over a prolonged period of time, but also promoted physical association of ODNs with tumor cells. In vivo modification of tumor cells will be beneficial for the local stimulation of antigen presenting cells such as dendritic cells responding to apoptotic/necrotic tumor cells. We also demonstrated a therapeutic benefit of this strategy by using a lipid-conjugated immunostimulatory ODN. This strategy could be immediately extended to many other functional ODNs, for example, immunostimulatory RNAs, siRNA, DNAzymes, or aptamers.

1. demonstrated a facile and simple method for cell modification with membrane anchored ODN

- not only promoted an in situ membrane insertion
- but also promoted physical association of ODNs with tumor cells

↓

2. beneficial for the local stimulation of antigen presenting cells

↓

3. also demonstrated a therapeutic benefit of this strategy

How the key argument(s)/technology(ies) are supported in the paper?

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anchor, we first characterized the tumor cell membrane insertion efficiency of several types of lipophilic ODNs in vitro. Fam-labeled single-stranded 20-mer oligonucleotides

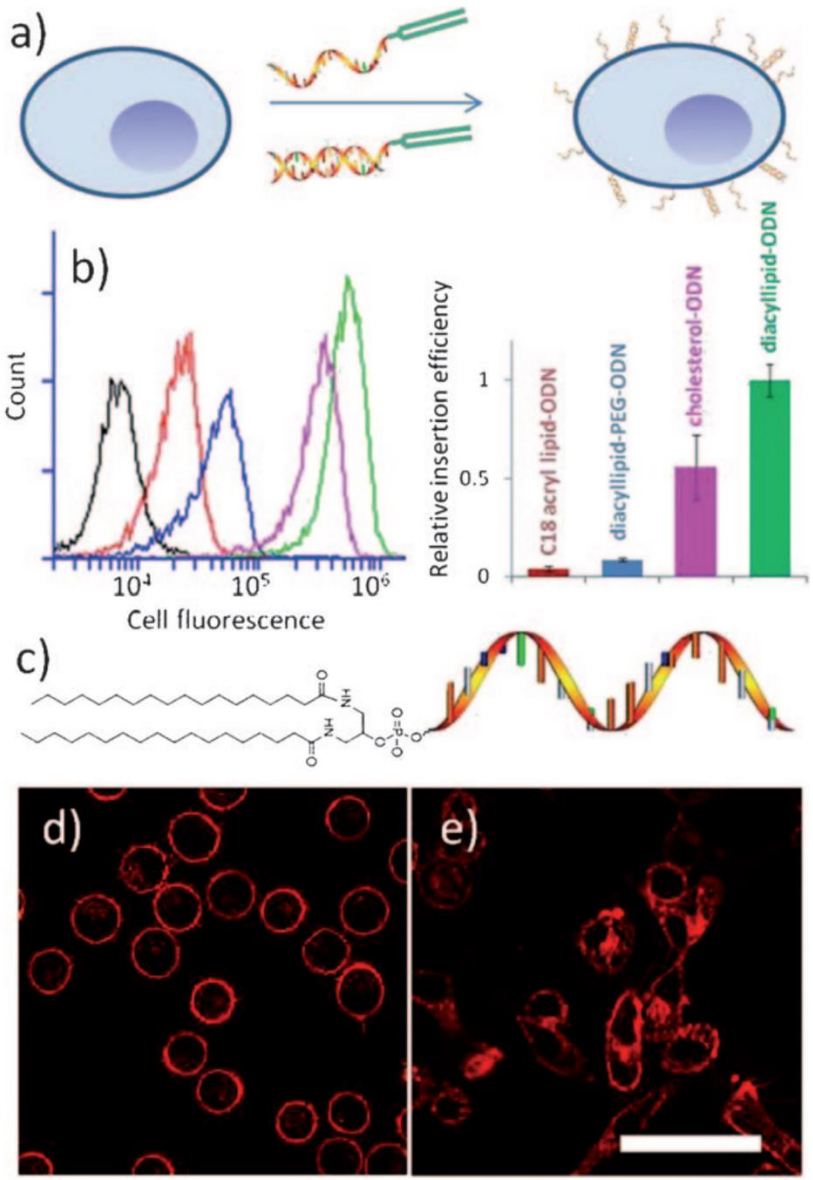

Figure 1. In vitro screening for optimal ODN conjugate structures. a) Schematic illustration of lipophilic-ODN insertion into cell membranes. b) Flow cytometric evaluation of membrane anchoring efficiency by different liphophilic modifications, left: flow cytometry histograms. black: untreated B16F10 cells, red: C18 single chain lipid ODN, blue: diacyllipid-PEG-ODN, purple: cholesterol-ODN and green: diacyllipid-ODN. Right: relative insertion efficiencies of each ODN conjugate based on the mean fluorescence intensity. c) Molecular structure of diacyllipid ODN. d) Confocal image of diacyllipid ODN-modified B16 cells. e) After 2 h of culture at 37 °C, a partial internalization of ODNs can be observed. Scale bar: 50 μm.

How the key argument(s)/technology(ies) are supported in the paper?

1. demonstrated a facile and simple method for cell modification with membrane anchored ODN

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- ➢ but also promoted physical association of ODNs with tumor cells

anchor, we first characterized the tumor cell membrane insertion efficiency of several types of lipophilic ODNs in vitro. Fam-labeled single-stranded 20-mer oligonucleotides

We then set up experiments to test whether in vivo cell membrane insertion would promote prolonged retention of ODNs at a tissue site. Following a common strategy to

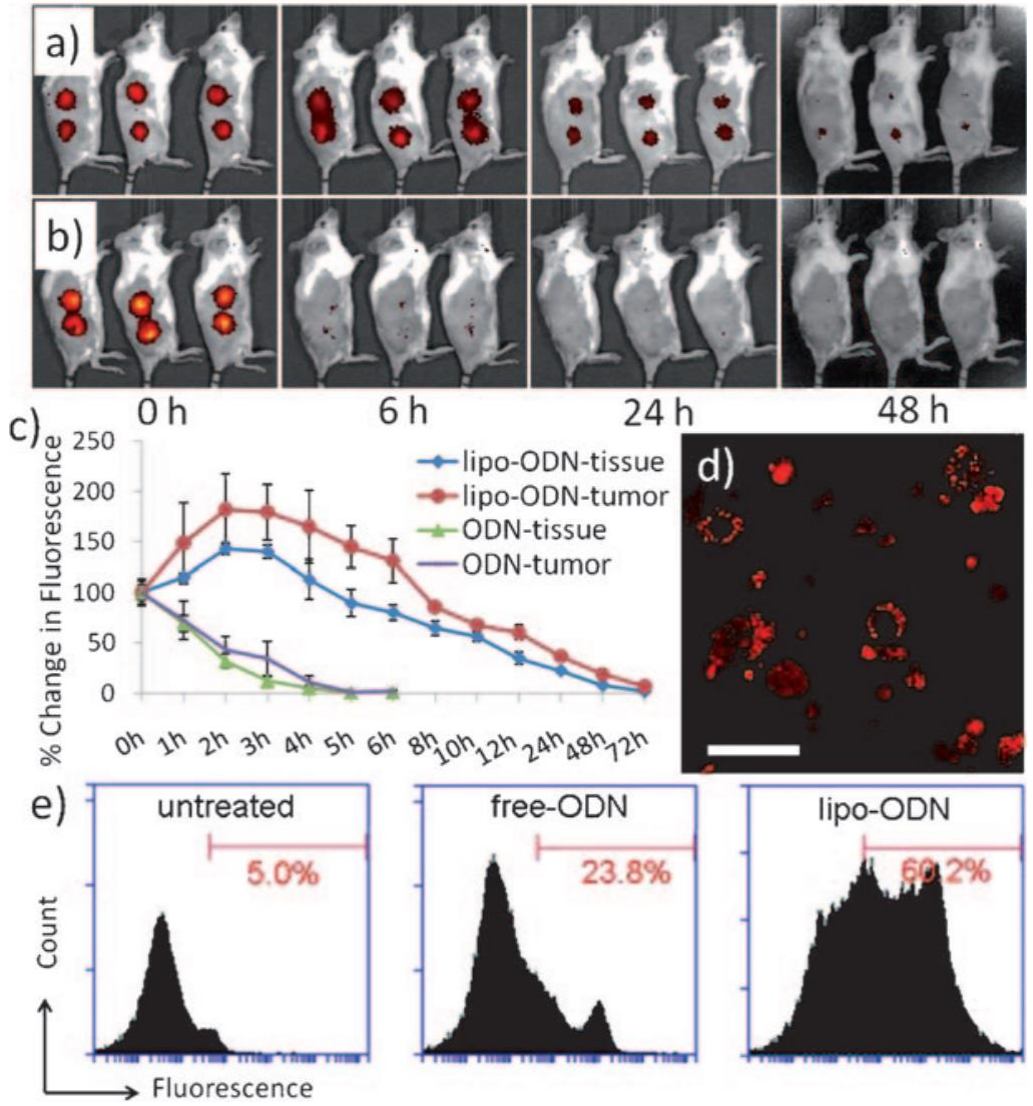

Figure 2. In vivo cell modification by lipo-ODNs. a,b) In vivo kinetics of fluorescence decay of rhodamine-conjugated lipo-ODN (a) and non-lipidated ODN (b). The upper sites on mice were subcutaneous injections into healthy tissue; the lower sites were intratumoral injections. c) Quantification of total fluorescence over time from IVIS whole-animal imaging of injection sites. d, e) Representative confocal image of tumor cells recovered from an intratumoral injection site (d) and flow cytometric analysis of recovered tumor cells (e) 3 h after injection. Scale bar: 50 μm.

How the key argument(s)/technology(ies) are supported in the paper?

1. demonstrated a facile and simple method for cell modification with membrane anchored ODN

- not only promoted an in situ membrane insertion
- but also promoted physical association of ODNs with tumor cells

2. beneficial for the local stimulation of antigen presenting cells

3. also demonstrated a therapeutic benefit of this strategy

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We then set up experiments to test whether in vivo cell membrane insertion would promote prolonged retention of ODNs at a tissue site. Following a common strategy to

Figure 3.

To determine whether enhanced tumor cell association/ retention at tumor sites could enhance the therapeutic efficacy of immunostimulatory ODNs, we next turned our attention to an unmethylated CpG single-stranded DNA oligonucleotide. CpG ODNs containing cytosine-guanosine

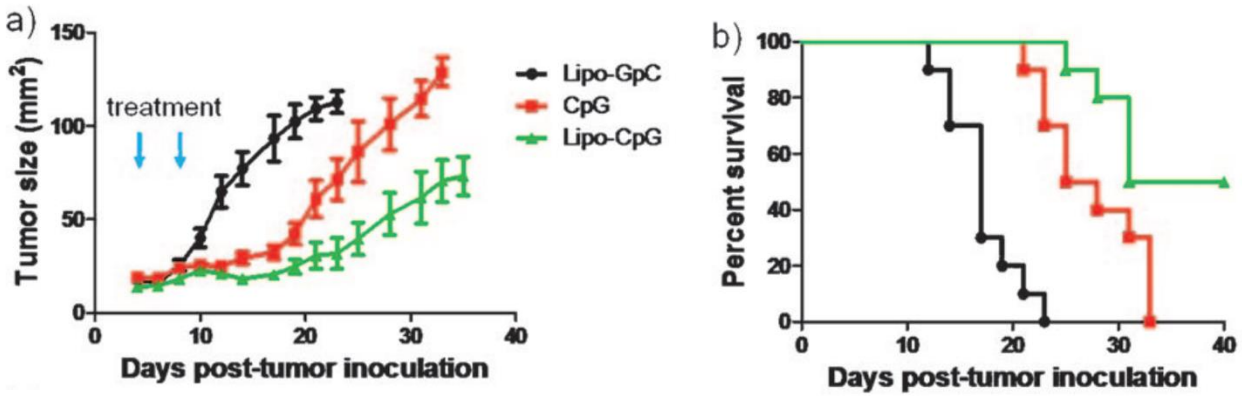


Figure 3. Therapeutic effects of lipid modified CpG ODN. a) Time course analysis of tumor growth ($n = 10$) after treated with two injections of either lipo-GpC, CpG or lipo-CpG. The differences for the treatment of lipo-CpG versus CpG were statistically significant ($P < 0.004$, paired t-test). b) Kaplan–Meier survival curve (with log-rank test) after treated with ODN probes, tumor-bearing mice treated with lipo-CpG have a prolonged survival compared with CpG group ($P < 0.01$).

Critical review of the main claims:

What has been shown *experimentally*:

1. Chemical structure improvement of ODNs
2. Therapeutic benefit

What is *hypothesized* in the discussion part on future applications:

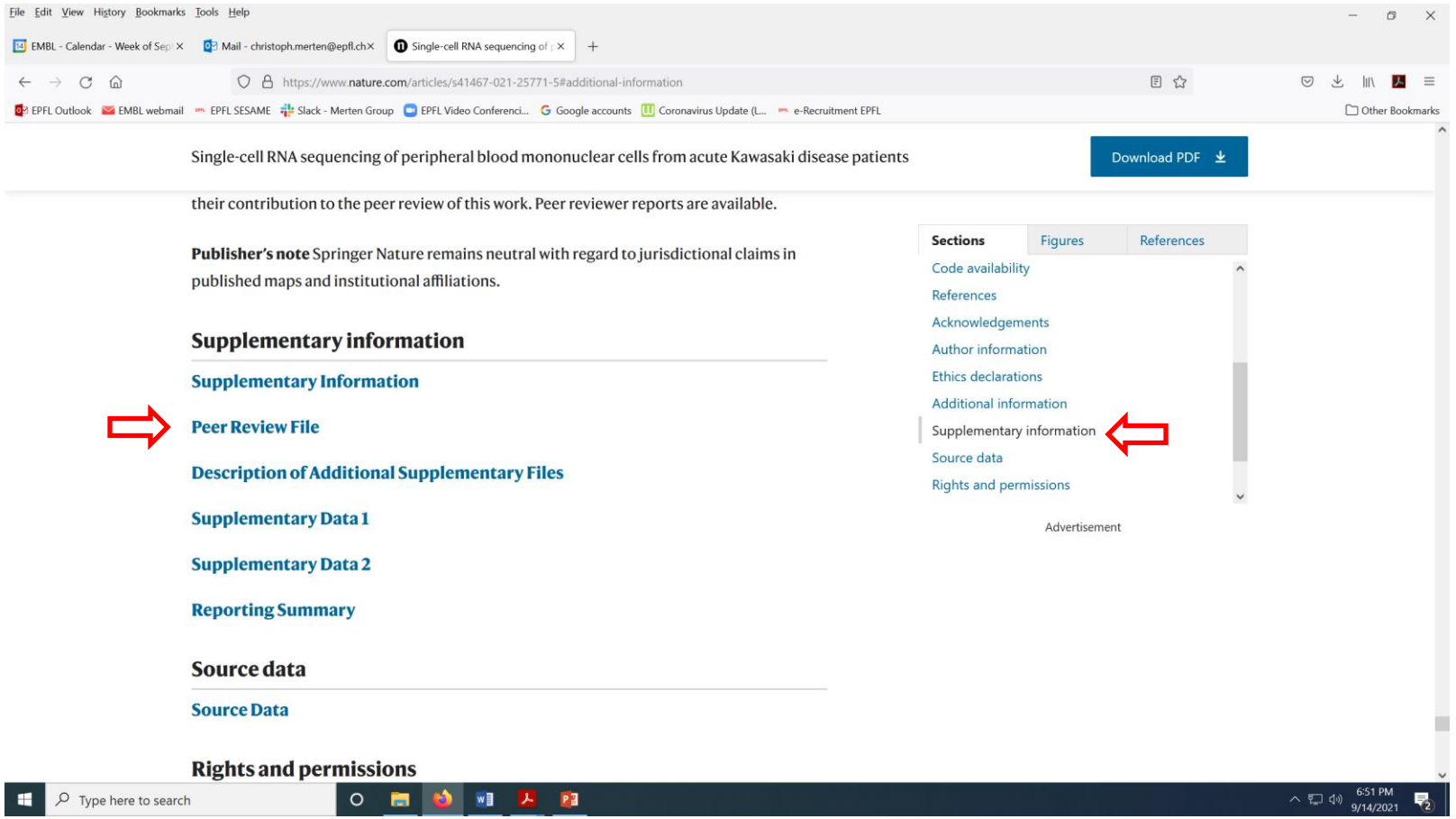
immunostimulatory ODN. This strategy could be immediately extended to many other functional ODNs, for example, immunostimulatory RNAs, siRNA, DNAzymes, or aptamers.

How to get second opinions and to measure impact:

1. Reviewer's comments – not (yet) available for Angewandte papers, but optionally published in e.g. Nature Journals
2. Papers citing this paper (how many? How do they judge the work?)
3. Following papers from the same group (did they implement any of the future applications described here?)

Be careful with claims that are not directly supported by experimental results (e.g. in the discussion part). Sometimes preliminary PoCs are used to claim something much bigger (e.g. a small effect in a particular mouse models is sold as a potential cure for all human cancers). Do NOT simply believe in everything the authors write, but rather get second opinions!

Going through (publicly available) Reviewer's comments. Example: **Single-cell RNA sequencing of peripheral blood mononuclear cells from acute Kawasaki disease patients** Wang et al., NCOMMS 2021, https://doi.org/10.1038/s41467-021-25771-5



REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):

In this manuscript, to better characterize the immune response and the transcriptional changes at the single-cell level during Kawasaki Disease (KD), Wang et al. perform single-cell RNA sequencing (ScRNA-seq) analysis of peripheral blood mononuclear cells (PBMCs) isolated from 4 KD patients at 2 different timepoints: during the acute phase and in the convalescent phase (24 hours after IVIG treatment). Similar analysis is performed on PBMCs collected from 3 healthy controls. Based on ScRNA-seq and a flow cytometric analysis of another dataset of KD and IVIG treated patients, the authors show that transcripts of B cells are increased during KD acute phase and significantly decreased in the KD convalescent patients and healthy controls. On the other hand, transcripts related to CD8 T cells and NK cells (although not significant) are decreased during acute KD and this result seems to be confirmed by flow cytometry. By performing BCR and TCR sequencing, the authors show that antibodies are involved in the convalescence phase and that there is no TCR clonal expansion indicating further that KD is not triggered by a superantigen. Although, the participation of the described cellular subsets to KD development has been already previously suggested, this is probably the first study attempting to characterize by ScRNAseq the immune cells involved in KD and during KD convalescent phase. However, this study is largely "descriptive" and has limitations, such as the small number of KD patients involved in the ScRNA-seq study and variability among the results, the lack of depth of the ScRNA-seq analysis, and the fact that the observed changes with the ScRNA-seq are not confirmed at the cellular level on the same patients by the flow cytometry analysis.

…let’s apply these concepts in the first course module!