What is the Living Materials project?

The Living Materials Square Table was a collaborative effort between the National Cancer Institute (NCI) and the National Science Foundation (NSF) to host a workshop on defining current work on, and envisioning the future of, Living Materials. Leading minds in Biomaterials, Cancer Biology, and Synthetic and Systems Biology were brought together in a virtual space to define the field of Living Materials as well as provide a roadmap for future research.

Why did we hold such a workshop?

We wanted to provide a platform for stimulating discussions between researchers at the frontiers of their disciplines. We surmised that this vibrant exchange of knowledge, thoughts, and ideas would identify research directions transformative for new materials design and cancer research. We envisioned one outcome to be an intellectual roadmap of challenges and opportunities for the two funding agencies to use in developing future programs.

Who led the approach?

Germano Iannacchione (NSF)
Shadi Mamaghani (NSF)
Kris Sunderic (NCI)
Nas Zahir (NCI)

Three Co-Chairs were recruited to represent and lead three focus areas. Co-chairs were selected for their expertise in their respective fields, their leadership qualities, and their collaborative spirit.

- Shannon Mumenthaler (USC) – Cancer Biology
- Shelly Peyton (UMass Amherst) – Biomaterials
- Krishnendu (Krish) Roy (Georgia Tech/Emory) – Synthetic and Systems Biology

A group of talented postdocs were also invited to fully participate in the workshop. They identified critical gaps in cancer research and provided a summary of questions they considered to be the most interesting to explore in the context of “Living Materials”. A compilation of their workshop notes is integrated throughout the report as well as linked in its entirety in a specified section below.

Meeting Host / Facilitators

KnowInnovation
Who is the audience for this report?

The community who works in the research spaces of Cancer Biology and Therapies, Biomaterials, and their applications, Synthetic and Systems Biology, materials scientists in general that could take inspiration from the cancer-motivated questions posed here, as well as the NCI and the NSF.

Summary of the report

The “Living Materials” Square Table (SQT) was a collaboration between the NSF and NCI leadership and the facilitator, KnowInnovation, who created a framework for this workshop. Co-chairs were recruited to represent the respective sides of the Square Table: Cancer Biology, Biomaterials, and Synthetic and Systems Biology, with a fourth side reserved for representatives from NSF and NCI funding agencies. Participants were identified based on their research background and expertise aligning with at least one side of the table. Prior to the start of the meeting, questionnaires were sent to all participants to elicit high level questions in the context of living materials and cancer, and the co-chairs helped organize the submissions into themed clusters.

Pre-Workshop: Questionnaire

1. What do you consider to be a useful or starting definition for “Living Materials”?
2. Looking 10-15 years into the future, what do you consider to be the most interesting question(s) (list 1-3 questions) that you think we should be exploring at the intersection of Cancer, Biomaterials, and Synthetic and Systems Biology?

On Day 1, small groups of participants were assigned one of these themed clusters of questions, and they were tasked with creating a title, converging on the most interesting questions from the collection. On Day 2, participants were asked to consider and prioritize what antecedent research would be necessary to address the high-level questions chosen from Day 1. On Day 3, participants were asked to identify what resources and infrastructure might be needed to conduct the ordered antecedent research. In the end, the “Living Materials” SQT format stimulated creativity, idea generation, and divergent thinking that may be transformative for cancer research and beyond. Several far-reaching ideas emerged from this workshop and are summarized below.

Structure of workshop days

SQT Day 1: Generate High Level Questions

Questions submitted by participants were grouped into seven (7) themes by the co-chairs:
SQT Day 2: Develop Antecedent Research
Participants in each group filled out a google document that included the following prompt:
To have [add your high-level question], we must have [fill in planned antecedent research in order of priority].

SQT Day 3: Identify Resources and Infrastructure
Participants considered the necessary resources and infrastructure to make the antecedent research as productive as possible, which ranged from tangible to intangible items, including hardware or other technology, training, community building, ethics, legal, standard-setting, etc.

Synthesis
Based on participant discussions over three (3) days of virtual sessions and captured on the KIStorm.com web platform, a synthesis of ideas by this research community emerged. Common terminology used to describe “Living Materials” was captured in a word cloud. Several focus areas are called out along with pertinent technology and resources that need to be developed.

LIVING MATERIALS

- Measure physical and chemical properties of disease matrix to design biomaterials
- Develop biosensing tools
- Logic gate sensors
- In situ assembling biomaterials
- Delivery methods
- Disruptive technologies in imaging

- Sense
- Decide
- Control

- Restore organ normalcy while stopping tumorigenesis
- Engineer cellular and non-cellular collectives with anti-tumor functions
- Use material to control (spatially and temporally) immune cells
- Rejuvenation of ECM to halt cancer
- Reverse-Engineer Control, Learn Assembly
Far-Reaching Takeaways from Co-Chairs:

1. How could living materials help us create a detailed spatio-temporal atlas of tumors with single-cell level details and map the interactomes? How do these interactomes evolve over time, age, lived experiences, diet/nutrition/microbiota, etc.? How can we do the same for ex vivo tumor models and connect the two together through Living Materials? What new materials, measurement techniques, and engineering tools need to be developed to enable this?

2. How might we create living materials through synthetic biology that can interrogate, measure, modulate, and treat tumors in vivo, and/or support, interrogate, and treat tumor models ex vivo? How do we validate the accuracy, sensitivity, and specificity of such living materials?

3. How might we create the computational framework and infrastructure to connect single-cell level multi-omic spatiotemporal data from tumors and tumor models to patient-outcome data, patient’s systems-level biological data, and/or a patient’s socioeconomic and lifestyle data (genetic and zipcode influence) to create predictive models?

4. How might we exploit the microbiota in tumors or in metastatic niches to shape the material microenvironment and guide or halt tumor progression?

5. How might we leverage artificial intelligence and other computational tools to study a finite number of patient-derived avatar responses to advance personalized medicine - i.e., study a minimal set of avatars to be able to accurately predict the patient’s response?

6. How might we use synthetic biology to engineer immune-therapeutic cells to interact with materials surrounding tumors - to infiltrate tumors more effectively and effectively kill cancer cells while avoiding suppressive signals from the material microenvironment?

7. How might we leverage the tumor microenvironment and tumor-host interactions to create the next generation of responsive, evolving, living materials that can sense, decide, and even control a tumor? How might we fool cancer cells and make them...
sense that they are in the 'wrong' microenvironment? Can we generate soil disruptors?

8. How might we create living materials that could treat a tumor and subsequently regenerate healthy replacement tissue, *i.e.*, the material function "evolves" with disease state?

9. How might we rejuvenate the material microenvironment around a tumor to restore organ normalcy while halting tumorigenesis?

10. How might we develop a "periodic table" of cellular and non-cellular interactions (*e.g.*, cell-cell and cell-material) to help guide the creation of relevant and predictive *in vitro* tumor models?

11. How might we apply the knowledge gained in using novel materials for cancer to other cellular and molecular systems? All the questions posed are relevant to many disease conditions and "normal" physiology. Thus, it is important to develop materials that can broadly answer these questions across multiple physiological and pathophysiological models.

12. How might we develop quality control and quality assurance metrics for living materials to ensure their reproducibility, scalable manufacturing, and broader translation?

Summary from the Next-Generation of Scientists (Postdocs):
As mentioned, post-doctoral scholars were invited to participate in the workshop, and they set aside time to discuss in their own groups the most exciting research ideas from the meeting. What emerged from their discussions were several key knowledge gaps in cancer research that this square table may be primed to address:

1. We are missing temporal information across scales (*i.e.*, at tumor and patient-level). We are currently making decisions with only discrete time snap-shots available to us.

2. We are missing the minimal necessary attributes needed to predict clinical outcomes.

3. We are missing universal controls, mutually agreed upon definitions, and data standards.

Several topics/questions were debated within this framework:

1. How can we leverage synthetic biology to create better probes to survey the material microenvironment around a tumor? How do we engage multiple disciplines to work together to develop the necessary sensors and tools?

2. How do we ensure that the diversity of disciplines is incorporated in the data collection process (*e.g.*, race, ethnicity, and environmental toxins)?

3. How can cancer influence how we, as a field, design new materials? If you have materials that act like cancer, what would that look like?

4. How can we create therapeutics to target cancer cells? How can we develop a material to deliver a therapeutic to target the material microenvironment rather than directly to the cancer cell?

5. How can we leverage the microbiome at the intersection of all 3 disciplines? *Cancer bio* - can the microbiome serve as a patient avatar of sorts given its involvement in a patient’s health status. *Synthetic bio* - can we engineer microbes for cancer detection and treatment. *Biomaterials* - can microbes or microbial biofilms serve as the living materials.
Scoping the problem: pre-workshop questionnaire

We started by identifying core themes of interest to the community. We did this through an online questionnaire designed to elicit participant views of the most interesting questions that might be addressed in Living Materials in the next 10-15 years. We asked participants how they defined “Living Materials”, what questions they thought we should be exploring in the near future that would accelerate both fundamental and translational science at the intersection of materials and cancer biology. No intellectual limits were placed, and questions were open ended:

3. What do you consider to be a useful or starting definition for “Living Materials”?
4. Looking 10-15 years into the future, what do you consider to be the most interesting question(s) (list 1-3 questions) that you think we should be exploring at the intersection of Cancer, Biomaterials, and Synthetic and Systems Biology?

Ahead of the meeting, we also provided the participants with a reading list to help them brainstorm these questions. These were not meant to limit nor promote any one point-of-view prior to the meeting. Rather, this was to simply illustrate the new and widely varying approaches and current thinking on “Living Materials”:

**Wyss Institute - Living Materials**  
https://wyss.harvard.edu/media-post/living-materials/

**DARPA - Engineered Living Materials (ELM)**  
https://www.darpa.mil/program/engineered-living-materials

**MIT- Hybrid Living Materials**  
https://www.media.mit.edu/projects/hybrid-living-materials/overview/

**NSF - Engineered Living Materials**  
https://nsf2026imgallery.skild.com/entries/living-materials

We also shared two keynote addresses from NSF (Sean Jones, Assistant Director of Mathematical & Physical Sciences Directorate) and NCI (Jennifer Couch, Chief of Structural Biology & Molecular Applications Branch).

We received over 75 questions from the participants, and the co-chairs of the meeting selected a few of the most exciting and far-reaching questions posed and presented them to the full group. This helped set the stage and tone for the workshop. A list of all the questions received are in Appendix I. Example questions are appended below.

1. How might we fool cancer cells and make them sense to be in the ‘wrong’ microenvironment?
2. How might we understand the critical early changes in the local microenvironment that determine the outcome of tumor initiating events? As the ability to build normal tissues improves, modeling the onset of tumor development and recapitulating the steps of early disease in the context of normal tissue will allow for interrogation of how early tumor-stroma crosstalk alters the local environment.
3. How might we understand the impact of the microbiome on cancer growth and response to therapy and how to manipulate microbiome interactions to enhance therapy effectiveness (for example transplants from long-term versus short term survivors produce effects on tumour growth via interactions with macrophages so building on this idea).
4. How might we use biomaterials, synthetic biology, and systems biology to understand tumour evolution and potentially control or inhibit evolution to ensure longer responsiveness to therapy?
5. How might we engineer fully synthetic biomaterials to act like cancer?
6. How might we determine what a personalized biomaterial might look like?
7. How might we use principles from synthetic and systems biology to "train" materials behavior?
8. How might we use AI to better iterate through systems design?
9. How might we engineer biomaterials to inform biology in real-time?
10. How might we design practical materials for cancer therapy that incorporate logic gates?
11. How might cells integrate environmental signals into a coordinated phenotypic or molecular response?
12. How might materials replace cellular therapies?

We then sorted all the questions received into broad research themes, first via a word-search dendrogram technique (Figure below), and then with feedback from all three co-chairs.

This process left us with 7 broad research themes, with 4-12 questions in each theme.
At the first square table session (March 30th, 2021, 1-4pm EST), the participants (along with co-chairs) explored, added to, and refined the questions in the clusters from Figure 2. At this first session, participants split into small groups and defined research clusters made by the organizers ahead of time, with the goal of discussing the questions and giving the cluster a name. After a short break, groups reconvened and chose the questions within that cluster that they considered to be most interesting. Participants were then asked to reflect overnight and return the following day with what research might be necessary to address those high-level questions.

As part of this session, participants were also asked to post “Audacious”, far-reaching, but potentially impactful questions, and create a “wish-list”. Five such questions were generated and are listed below:

1. Could we reprogram T-cells to modify matrices, so they can make their own paths toward tumors?
2. There are dogs that can be trained to smell cancer (old fashion AI). Do we know what they are smelling? Can we create a biomaterial that can detect it?
3. Can we test cancer’s responses to all biomaterials? Predict its responses to all matrix environments?
4. Why do metastases of a tumor tend to look like the primary tumor from a histopathological point of view? Histological memory? Can we understand and exploit this for therapy?
5. How might we engineer an immune "super cell" capable of taking the best parts of each cell type into context-dependent action?

Several of these audacious questions were incorporated in the questions generated during day 1. The overall output from day 1 was a portfolio of high-level questions which, if answered, might lead to a step change in the science of Living Materials. Within the clusters (Figure 3), groups generated dozens of questions. Groups were shuffled, and these diverse sets of questions were then narrowed to those the new groups found the most interesting, which helped define the 6, named clusters more clearly:
RED GROUP ONE

Extracellular environment of pre-cancerous and cancerous progression.
- How might we define the extracellular and tumor microenvironmental factors that influence the transition of early lesions into more aggressive cancers?
- How might we functionally define extracellular matrix heterogeneity and further embrace this complexity in experimental design and simulations?

No more room on this one, please choose another!
4 people in total

ORANGE GROUP ONE

How might we recreate tissue environments with crucial components of cancer to provide valid models for specific research questions, and how do we know when we are wrong?
- How might we incorporate and/or better understand the influence of ancestry, gender, and/or lived experiences into our models?
- How might we develop a "periodic table" of cellular interactions (e.g. cell-cell and cell-ECM) to help guide the creation of relevant in vitro tumor models?

Click to sign up...
2 people in total

AQUA GROUP ONE

Living Materials as Therapies: From Engineered Immune Cells to Cellular Collectives.
- How might we engineer "cellular collectives" with anti-tumor functions?
- How might we create a living material that could treat a tumour and subsequently regenerate healthy replacement tissue?
- How might we use a localized, programmable material to control (temporally and spatially) engineered immune cells to control immunotherapy?

No more room on this one, please choose another!
4 people in total

YELLOW GROUP ONE

Harnessing the power of computational approaches to tackle the combinatorial explosion of cancer.
- How might we develop a detailed, multi-scale atlas of the spatio-temporal features (cells, ECM, biophysical and biochemical properties, connectome, omics) of the tumor microenvironment for various human cancers - across gender, ethnicity, age, socioeconomic groups?
- How might we use the Atlas and computational framework to develop systems and synthetic biology tools and materials to program, continuously measure and monitor, and control tumors - which then informs and improves the Atlas and computational tools?
- How might we develop computational and experimental models that provide detailed understanding across scales of interactions within the tumor microenvironment, between the host and the tumor, and between the host and the external environment (e.g. socioeconomic status, nutrition, lifestyle)?

No more room on this one, please choose another!
4 people in total

BROWN GROUP ONE

Living materials as patient specific avatars for predicting outcomes and therapeutic responses.
- How might we create the most accurate patient-specific living cancer avatars reproducibly, efficiently and cost-effectively - that can consistently predict patient responses? What is the minimal set of features necessary to fully recapitulate the complete patient response, including patient diversity (socioeconomic and environmental variables).
- How might we leverage artificial intelligence and other computational tools to study a finite number of patient-derived avatar responses to advance personalized medicine - i.e. study a minimal set of avatars to be able to accurately predict the patient's response.

No more room on this one, please choose another!
4 people in total

GREEN GROUP ONE

Synthetic materials as cell-free TME-normalizing therapeutics.
- How might we leverage study of the tumor microenvironment and tumor-host interactions to develop (reverse engineered), the next generation of responsive, evolving, living materials that can sense, decide, and control the tumor?
- How might we create programmable living, responsive materials or materials that can "learn" to interact with cells for short- and long-term sensing, diagnostics, and control. How might we modularize these living functions of the materials?
Square Table Session 2, Developing Antecedent Research Questions

At the second Square Table Workshop (March 31st, 1-4pm EST), participants explored what antecedent research might be required to answer the questions generated in Figure 4. Participants could choose which research questions they were most excited to discuss, with a maximum of 4 participants per group. Those groups then reported back to the entire workshop the discussions they were having, before going back into groups (with some re-shuffling at the direction of the co-chairs to ensure groups had all the necessary complementary expertise) to solidify their antecedent research questions. Participants were directed specifically to discuss and agree on what antecedent research is required to support each high-level question, and in what order it should be conducted. At the end of Day 2, participants were encouraged to use the next few days to reflect on what resources might be necessary to conduct the antecedent research.

We have summarized thoughts from one of those groups (Red) as an example of the topics discussed:

Red Group:
Q1: How might we define the extracellular and tumor microenvironmental factors that influence the transition of early lesions into more aggressive cancers?

Needs: 1) Define the components of “normal tissue” more completely and more broadly. 2) Determine how environmental drivers (e.g., diet, stress, age, race/ethnicity/gender) shape ‘normal’ tissues that will change the baseline and potential response to an initiating event. 3) Increased representation in our tissue banks. 4) Real-time sensors to complement endpoint experiments. 5) Disruptive technologies in imaging. 6) Increased bio-orthogonal approaches - get ‘all the things’ from one experiment (for example, capture RNA/protein/biophysical information)

Antecedent questions:
Can this provide information on the interface between the tumor cell and microenvironment that provide insight into why some tumors progress and others don’t?

The microenvironment is constantly evolving - how do we capture/model ECM deposition/cross-linking/degradation, cell phenotype/plasticity in a controlled manner?

The timescale of early tumors is probably one of the slowest - how do we model this in a tractable way - ‘simulate the long game’ - what can be learned from the field of biology of aging? Increased cellular models that reflect the age of the cancer patient population of interest?

Q2: How might we functionally define extracellular matrix heterogeneity and further embrace this complexity in experimental design and simulations?
Needs: 1) Capture information that links changes in the local scale to the bulk. 2) Experimental design approaches that allow fuzzified/non-precise models. 3) Population level data to understand risks at the population level that match to molecular level changes/baselines.

Antecedent questions:
How do we do multiple perturbations - do we need to separate two co-occurring events to identify which is key? Or can we embrace that we don’t need to know everything to make useful predictions?

How do we use models to identify where we need sensors?

If we get ‘all the data’, how do we make sense of it - how do we sort out what changes are drivers vs. bystanders?

Can we characterize the effect of therapies we use for cancer on the niche - can we study this to find a way that is supportive of normal tissue re-establishment vs. activation of remaining cells?

Square Table Session 3: Identifying Necessary Resources and Infrastructure

At the third and final Square Table Workshop, we tasked participants with identifying the resource and infrastructure needs that would be necessary to undertake the research questions they posed in days 1 and 2 of the workshop. Co-chairs first invited the participants back to the final day of the workshop, thanked them for their time, and charged them with a final refining of their research questions. We reminded them of the goal of maintaining a focus on the 10-15 year horizon. After approximately an hour of this refinement, groups presented back their narrative to all participants. We then asked them to identify those things (both tangible and intangible) that might be required to undertake the proposed research.

What emerged beyond cancer

A significant focus of the workshop was on how living materials can be used to better understand and treat cancer. However, we also captured information on how our understanding of cancer can help develop living materials for other diseases or applications. Our knowledge of what has gone awry in cancer, from cellular to non-cellular information exchange, can support the development of disruptive technologies to achieve “normalcy”.

A key take away was the identification of a critical need for developing detailed spatio-temporal atlases of tumors and tumor models that not only includes spatio-temporal omics information, but also includes age, sex, race, ethnicity, and socio-economic variables. How can we then connect the real-world human atlas with the in vitro models through living
materials? This underscores the need to develop new technologies, computational and data analytical methods, and open access to data across the community that goes far beyond cancer and can be emulated in other diseases.

Another key aspect is how we can leverage synthetic biology and fundamental materials science and engineering to create unique and unprecedented new materials that can sense and report on their microenvironment and “evolve” their properties with time from being a therapeutic to being a tissue-healing material. Development of responsive, multi-functional, and potentially in-situ evolving synthetic or nature-derived materials can be tailored for specific physiological and pathophysiological environments and would have broader applications beyond cancer.

A fundamental issue is reproducible and quality-controlled manufacturing of disease models, therapeutics, and diagnostic probes, at scale. One-off complex synthesis/fabrication of organoids, on-chip devices, therapeutics, and probes does not provide reproducible, usable high-quality tools for the broader community and hinders translation. Appropriate scalable manufacturing platforms with well-defined quality control and quality assurance (QA/QC) metrics must be developed which would increase data reproducibility, adoption of technologies and methods across research fields, and ultimately impact translation to industrial and clinical practice.

An additional key aspect of the Square table that transcends diseases and disciplines is that of workforce/researcher training. Solving the problems outlined here requires highly multidisciplinary training that spans materials science, systems biology, computational methods, synthetic biology, and physiology/disease-pathology. It is imperative that we develop best practices for providing such integrated, diverse training to trainees, especially at the graduate and postdoctoral levels.

**Perspectives from another generation**

Insights from the Post-Docs have been integrated throughout this report. A comprehensive collection of their notes and feedback can be found here:

**Our conclusions**

In summary, the “Living Materials” square table was a resounding success in collaborative engagement and idea generation. Here we provide additional feedback, improvement areas, and next steps.

**Constructive feedback/improvement areas:**

1. The antecedent questions discussion was too short, and the momentum was interrupted.
2. A need for clearer instructions as some groups were philosophical for a significant portion of the breakout sessions until a co-chair joined and brought someone new or redirected the conversation to move things forward.

3. It is important to diversify the groups and continuously check in to ensure the necessary expertise is captured to facilitate the discussions in each group.

4. Specific to “Living Materials”, the microbiome topic was dropped early on due to lack of expertise and engagement by the assembled community; however, it was clearly acknowledged as an important topic to pursue.

5. A need for more space to repeatedly “run things up the flagpole and tear them down” to encourage catalytic thinking.

6. Sustained meetings of this type (e.g., quarterly) are necessary to make the ideas more specific and actionable.

**Suggestions for next steps for this project:**

1. Small, focused working groups to address the far-reaching takeaways summarized by the co-chairs
   a. Bring thinkers together to stimulate the ideas that could deliver on the big goals

2. Identify additional participants for discussion with expertise in the microbiome, synthetic biology, and computational biology
   a. As acknowledged previously, “microbiota” as a topic area was underdeveloped due to a lack of expertise present at the square table. However, given their ability to manipulate materials and metabolism, and their ability to be manipulated (i.e., cargo carriers), microbiota may serve as a unifying framework that can be applied across disease applications for treatment. It will be important to devote significant attention to this area in follow-up discussions.

**EPILOGUE**

To end this report, we would like to feature a few participant comments captured in the feedback survey:

"A wonderful opportunity to meet researchers from new fields, as well as those in my field. I was very excited about the opportunity to think long-term about tackling the really big questions."

"The meeting is well organized with specific target guidelines so everybody can stay focused and on task. The time always felt too short, which only said how interactive and wonderful the discussions were."

"This was a wonderful opportunity to meet amazing scientists and brainstorm ground-breaking research needed to solve big problems in cancer."
Biomaterials at Division of Material Research:
https://www.nsf.gov/funding/pgm_summ.jsp?pims_id=505461
Physics of Living Systems at Physics Division:
Chemistry of Life Processes Program at Chemistry Division:
https://www.nsf.gov/funding/pgm_summ.jsp?pims_id=505564&org=CHE
Mathematical Biology Division at Mathematical Sciences Division:
https://www.nsf.gov/funding/pgm_summ.jsp?pims_id=5690&org=DMS&from=home