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EDITORIAL

How should bioinformatics PIs run wet-labs?

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With the rapid development of biotechnology, data-driven bioinformatics research is increasingly dependent on data generation from biological wet-labs. At the same time, to gain in-depth knowledge of various biological systems, conventional biology laboratories have become more reliant on the establishment and optimization of advanced bioinformatics methods. Many bioinformatics labs are debating whether to build their own wet-bench or to seek collaborations, while many wet-bench labs are also confused over whether they should build their own dry-labs or likewise seek collaborations. The YBP (Young Bioinformatics PIs) Forum held an online seminar and panel discussion entitled "Bioinformatics PI Running A Wet-lab: Opportunities and Challenges" on Jun 10, 2022. In this forum, three young bioinformatics PIs (Drs. Yiwen Chen, Gangqing Hu and Wanlu Liu) shared their experiences in establishing wet-labs, and four senior bioinformatics PIs (Drs. Xiaole Shirley Liu, Jing-Dong J. Han, Ting Wang, and Kaifu Chen) attended the ensuing panel discussion on the opportunities and challenges of running wet-labs (Table 1).

Table 1 Bioinformatics professors shared experiences in the 2022 YBP online seminar "Bioinformatics PI Running A Wet-lab: Opportunities and Challenges"

Name	Affiliation	Presentation title	Sessions
Yiwen Chen, Assistant Professor	The University of Texas MD Anderson Cancer Center	Building a 'humid' lab: an on-going lesson	Seminar & panel discussion
Gangqing Hu*, Assistant Professor	West Virginia University	Overseeing a moisture land in a state almost heaven	Seminar & panel discussion
Wanlu Liu, Assistant Professor	Zhejiang University	A song of wet and dry: poise on the balance beam 'gracefully'	Seminar & panel discussion
Xiaole Shirley Liu**, CEO	GV20 Therapeutics		Panel discussion
Jing-Dong J. Han, Professor	Peking University		Panel discussion
Ting Wang, Professor	Washing University in St Louis		Panel discussion
Kaifu Chen, Associate Professor	Harvard University		Panel discussion

* Organizer of the session and panel discussion moderator. ** Former Professor, Harvard University and Dana-Farber Cancer Institute.

We here summarize experiences and suggestions given by the presenters, to provide support for new PIs running wet-labs. The presenters also give some important hints for experimental postdocs and graduate students on applying for suitable positions or becoming excellent students.

BACKGROUND OF THE PRESENTERS

Yiwen Chen (Fig. 1) is an Assistant Professor from the Department of Bioinformatics & Computational Biology at the University of Texas MD Anderson Cancer Center. Before starting his career as a bioinformatics researcher, he got a bachelor's degree in Physics at Fudan University, China. After reading many interesting quantitative biological modeling papers, he realized that it may be time for a Biology Revolution just as the Physics Revolution happened in the 20th Century. Yiwen shifted his interests to Protein Structure & Dynamics and got his PhD degree in Physics/Biophysics at the University of North Carolina at Chapel Hill. During that time, he was still unfamiliar with conventional experiments of biology. He decided to receive his experimental training in a *Drosophila* lab from the Howard Hughes Medical Institute (HHMI) and Harvard Medical School. After feeding flies for one year, he noticed that next-generation sequencing was an emerging field with a potentially greater direct impact than model organism research on human health. He then took a computational biology & bioinformatics postdoc position in Xiaole Shirley Liu's lab (Harvard University and Dana-Farber Cancer Institute, USA). Based on his multi-disciplinary research background, he built his own lab at the University of Texas MD Anderson Cancer Center to focus on integrating computational and experimental approaches to decode post-transcriptional regulation.

Gangqing Hu (Fig. 2) is an Assistant Professor from Laboratory of Genomic Data Science and Epigenome Biology, Department of Microbiology, Immunology, and Cell Biology, West Virginia University

Figure 1. Yiwen Chen, Assistant Professor, The University of Texas MD Anderson Cancer Center.

Figure 2. Gangqing Hu, Assistant Professor, West Virginia University.

(WVU). After graduating from Peking University, he researched epigenomics in National Institutes of Health (NIH) for nearly 10 years. During those years, he witnessed a big trend in what was happening. Bioinformaticians were frequently exposed to wet/dry-labs for experiments training and wet-labs frequently provided positions for bioinformaticians. During the transition to a faculty, he realized that research at WVU was seeking strong bioinformatics supports, and epigenome studies were underrepresented in this research-intensive land-grant university. Based on above considerations, Gangqing Hu joined the faculty at WVU in the summer of 2019.

Wanlu Liu (Fig. 3) is an Assistant Professor from ZJU-UoE (ZJE) Institute, Zhejiang University, China. She transferred to the bioinformatics field as a student in medical school. During her undergraduate study, she learnt basic biological experiment skills from different labs. But she found she was not good at doing wet experiments. Before preparing her undergraduate thesis, she entered a functional genomics lab where she started to learn bioinformatics. She believed bioinformatics opened a door to a 'New World' for her. She pursued her Ph.D. degree at University of California, Los Angeles (UCLA) and began to study DNA methylation and epigenomics via bioinformatics analysis. Considering the development of her future career, Wanlu realized she must learn more wet experiment skills to start-up her own lab. From 2018 to 2019, she joined in UCLA as a postdoc to study stem cell biology. After joining ZJE in 2019, she started to run a wet and dry combined lab in order to deeply understand the stem cell epigenetics through wet experiment results and bioinformatics analysis.

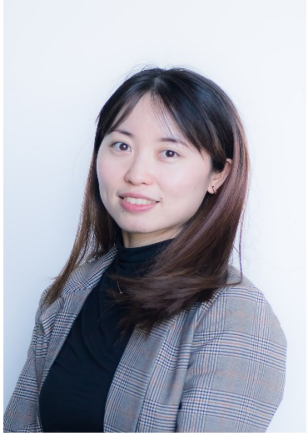

Figure 3. Wanlu Liu, Assistant Professor, Zhejiang University.

YIWEN CHEN'S EXPERIENCES

Experience 1: Three components for setting up a wet-lab

For bioinformatics PIs to run wet-labs, Yiwen mentioned that three main components should be considered when setting up a wet-lab from the very beginning. The first component involves defining the scope of your wet-lab work: that is, whether you want to simply validate the computational predictions; whether to study mechanisms; whether to perform large-scale profiling experiments on a regular basis; what experimental techniques are to be used. The second component is the search for wet-lab space/resource support as part of the start-up package (for junior faculties) or after receiving major external grants (for mid-career or senior faculties). The third component is estimation of cost of the necessary equipment, and subsequent purchase. Bioinformatics PIs can get advice from experimental PIs and feedbacks/comments from equipment users online/offline.

Experience 2: Leveraging external experimental resources

Considering the limitations of expertise of lab members in start-up labs, bioinformatics PIs should leverage external experimental resources. They can collaborate with experimental labs or pay-for-service from core

facilities and companies. When they decide to collaborate with experimental labs, the most important thing to note is the person you are going to directly cooperate with, this plays a key role in the success of collaboration. The nature of the collaboration should be clearly defined from the beginning. As for the pay-for-service, it is always straightforward and can provide a relatively defined timeline, but the experimental quality varies among different core facilities and companies.

Experience 3: Recruitment and mentoring of experimental postdocs

Yiwen thought PIs should define the qualification or skillsets for postdoc candidates, including which of these are 'must have', and should question whether candidates complement or are compatible with the skills, experiences and personality of the existing team. PIs should also conduct systematic screening of postdoc candidates. They can collect as much information as possible about each candidate's former lab, such as the culture of his/her former lab, the former advisor mentoring style, and relative performance of the candidate in the former lab. When PIs interview the candidates, they should scrutinize and be critical on experimental details in order to evaluate the capability of candidates. It is also important that PIs should evaluate the personality and motivation of candidates. After recruiting qualified postdocs, Yiwen usually encourages them to present and discuss 'negative' data. He thought PIs should try to be actively involved in experimental designs. If some problems cannot be resolved within the lab, PIs should seek help from experimental collaborators or external experts.

GANGQING HU'S EXPERIENCES

Experience 1: Keep happy when facing to difficulties

When Gangqing joined in WVU in 2019, he believed West Virginia must be a heaven for his new career just as in the song 'Take Me Home, Country Roads', which proclaims "Almost heaven, West Virginia." He envisioned that his new wet-lab should look like one with an experienced postdoc who is acting as a co-founder to drive experiments and train students. This lab should have a technician on-board as lab manager to coordinate lab activities, such as ordering, receiving, inventory, *etc*. Many students should be interested in joining in the lab, because they can learn bioinformatics methods to enhance their competitive advantages. The lab should receive strong and timely administrative support to assist on paperwork on hiring, purchasing, grants, *etc*.

As we know, the years since 2019 have been difficult, especially for new labs, because of the worldwide COVID-19 pandemic. It has been far tougher than Gangqing had expected. Despite facing this brutal challenge, he gave his advice with a smile. Because of this happy lab culture, Hu's lab attracted and kept nearly ten students and postdoc fellows.

Experience 2: The student can be trained in a mode of 'getting meals from 100 families' (BaiJiaFan)

When Gangqing set up his own lab in WVU, there was only one student recruited to his lab. He sent this student to his collaborators' labs to learn different wet-lab skills, such as cell culture, FACS, RT-PCR, ATAC-seq, RNA-seq and CRISPR KO. He encouraged his student to attend and make presentations in his mentor's lab meetings. It turns out that this student became excellent in the lab, with an out-going personality, willingness to help others, and a high level of independence.

Experience 3: Some strategies to minimize contamination in cell cultures

Cell culture is a basic biological skill in wet-labs, but contamination, especially by mycoplasma, can appear in cell culture rooms. To avoid such contamination, the first point is that a new cell line coming in must be tested for mycoplasma. Then the lab should periodically test for mycoplasma, say every three months. Additional test of mycoplasma must be done before doing expensive assay such as the 10X scMultiome. Hu's lab has accumulated a list of over 27 notes to minimize mycoplasma contamination.

Experience 4: Outsource or DIY

If bioinformatics lab wants to do a wet experiment, the PI should estimate cost of target assay. Gangqing mentioned PIs can search price information from many core facilities, or commercial quotes, or can evaluate the price of kits, reagents, and labor cost for in-house work.

WANLU LIU'S EXPERIENCES

Experience 1: From cognitive learning, associative learning to autonomous learning

Wanlu thought the philosophies of pure bioinformatics labs and wet-dry combined labs were quite different, in terms not only of team management but also of the gaps between wet and dry skillsets. Faced with these differences, she and her lab members started with 'cognitive learning'. They received basic wet-lab training from wet-lab collaborators. After mastering those basic skills, they started 'associative learning' to perform some advanced wet experiments. If some experiments could not be done in her lab, she helped her students to outsource expertise. She called this 'autonomous learning'. She also mentioned that every junior bioinformatics PI who wants to run wet-labs should keep a good spirit by lowering expectations, maintaining standards, and keeping patience.

Experience 2: Lab management

As for bioinformatics PIs who want to set up wet-labs, they will face more complicated issues than those faced by pure bioinformatics PIs, such as cost management, lab meetings, lab safety, lab duty, wet-lab driver, collaborations, lab inventory management, team growth and so on. Wanlu classified these issues into three categories as purpose, people, and process. As for 'purpose', she stated that junior bioinformatics PIs should identify wet-lab-oriented scientific questions, principally concerning the specific scientific questions that can only be addressed with wet-labs. For key 'people' in establishing wet-labs, young bioinformatics PIs should work closely with wet-lab collaborators while identifying the wet-lab 'driver' in the lab. Furthermore, PIs should focus on team growth. In her lab, she provides internal training/ workshops for every lab member to train hardcore skills and weekly one-on-one informal meetings to discuss career development, communication skills, and time management skills, to enhance soft skills of her team members. For the 'process' part, Wanlu mostly mentioned three sections: cost management, lab meetings, and lab duties. For cost management, there is a bi-weekly cost review with the lab manager to track the wet-lab costs. In addition, there are annual cost review lab meetings and annual budget planning for each ongoing project. For lab meetings, there are bi-weekly progress meetings or project brainstorm meeting. For lab duties, she suggested the general rules are establishing standard operating procedures (SOP) and spreading the lab duties evenly in the lab. For example, lab notebook management is organized by one of the lab's senior members, who is responsible for training junior students on how to write a good lab notebook and for managing the monthly backup of electronic version of lab notebooks.

Experience 3: Encourage students to identify their position

How do PIs encourage students in a dry-wet-lab to identify their position on the broad wet-dry spectrum? Wanlu believed that this should be based on students' self-motivation. As mentors, they should encourage students to try different wet or dry tasks and identify the field that they find most exciting to study. Mentors should provide students task rotation and collaborate with colleagues to accomplish projects. In the end, Wanlu suggested every junior bioinformatics PIs should learn to 'dance with uncertainty'. By establishing critical scientific questions, building a diverse team, and being open-minded to uncertainty, junior bioinformatics PI can experience joyful scenery along the journey of establishing wet-labs!

PANEL DISCUSSION

In the panel discussion, seven presenters shared their opinions on the following questions.

Question 1: Is it necessary to establish wet-labs for bioinformatics PIs?

Dr. Jing-Dong J. Han from Peking University suggested that whether to collaborate or to establish the experimental platform should depend on PIs' requirements. If PIs can easily find collaborators and experiments would not take a long time, they can collaborate fully with other wet-labs. If the experiments are necessary for the development of bioinformatics labs, PIs should establish the system for experiments. Dr. Ting Wang from Washington University in St. Louis gave advice that bioinformatics labs should consult and collaborate with wet experimental experts to solve the problems of experiments.

Question 2: How can wet-bench postdocs be attracted to join bioinformatics labs?

Dr. Yiwen Chen said bioinformatics labs lack advantage in competing for excellent wet-bench postdocs. Bioinformatics PIs could therefore consider other postdocs who had similar research background from unpopular research fields. Yiwen recommended Nature Jobs as a suitable place for postdoc recruitments because he usually received lots of applications after releasing a post. Former Professor from Harvard University Dr. Xiaole Shirley Liu thought bioinformatics labs should consider career development for experimental postdocs instead of only receiving experimental help from them.

Dr. Kaifu Chen from Harvard University also shared his opinion on attracting postdocs to join his lab, such as seeking help from collaborators.

Question 3: How to evaluate postdoc candidates?

Drs. Yiwen Chen, Gangqing Hu, and Wanlu Liu all suggested that collaborators should be invited to participate in the interviewing process.

Question 4: How to manage inventory?

All PIs in this seminar recommended ordering and management in MS excel can be easily adopted. Other professional inventory management systems such as Quartzy (free option available for academic use) for streamline lab operations can also be considered.

Question 5: How should wet-bench advantages be presented when bioinformatics PIs wanted to apply for grants?

Dr. Ting Wang said bioinformatics PIs can show the advantages of their collaborators who do the wet experiments or can submit the primary data to demonstrate their capability in solving the key biological problems.

At the end of the seminar, all participants confirmed that the future trend of bioinformatics labs would be combination of wet and dry components in labs. Although the process is tough, the experience will be rewarding.

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