

## Prof. Kewei Ma: a kind soul with a beautiful heart who lives without regrets

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### Introduction

The ancient Greek aphorism “*know thyself*” engraved on the forecourt of the Temple of Apollo epitomizes the human desire for the exploration into the unknown. In fact, never has mankind dragged their feet in understanding themselves, as in the achievements scientists have made all these years in the studies of disease and pathology.

Ere the 2017 WCLC journey, AME editors were sent across China to conduct in-depth interviews with an army of distinguished experts in the field of lung cancer. Together we learned how these soldiers fought for the nation that has the largest number of patients, and how they dedicated their lives to inventing the most-advanced weapons and probing into the enemy camp. From the past they reflect and learn from mistakes; at present they work hard and make changes; for the future they make plans and improvements.

May this issue take you to the innermost world of these Chinese scholars, where you can delve into their wealth of knowledge and be inspired.

Prof. Kewei Ma (*Figure 1*) was born in 1968 at the foot of White Mountain and is the eldest in his family.

Prof. Ma's life is tied closely to the word “Bethune”: his Bachelors, Masters and PhD were all completed in the Norman Bethune University of Medical Science, he did research at the Hong Kong University of Science and Technology (HKUST) after working as a cardiothoracic surgeon in First Clinical Hospital, Jilin University for 5 years. In 2006, as a physician, he was involved in founding the Norman Bethune Thoracic Cancer Multidisciplinary Team and the Norman Bethune Thoracic Disease Center, and pioneered research work in lung cancer EGFR mutation detection guided target therapy.

He has gone from surgery to internal medicine, from clinic to research and back to clinic, and devoted himself to laboratory work for more than 4 years. After his many experiences, Prof. Ma has his own principle he abides by: “Do whatever is required, and do it as well as possible”.

In his time studying in Hong Kong, Prof. Ma's research

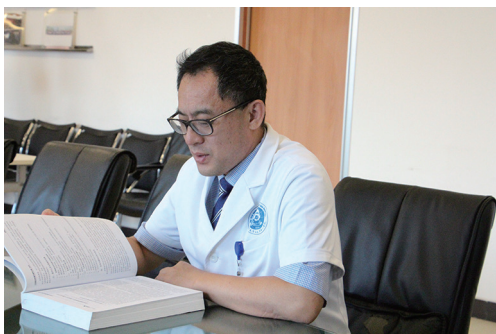


**Figure 1** Prof. Kewei Ma.

field was the regulation and control of cancer cell signal transduction pathways. This experience not only allowed Prof. Ma to carve himself a figure later in signal transduction related work, but also allowed him to develop a habit—no matter the creation of a new targeted drug, or the resistance of a targeted drug, he can always find out where the ‘root’ is, and is always tracing the source of any problem.

This is not unrelated to his ‘fitting’ choice back in the day. Prof. Ma takes pride in this. He told us that his choice was made because a few consecutive Nobel Prize winners at that time were researchers in the field of signal transduction pathways. Here, he dropped a hint to the readers: the Nobel Prize winners in recent years are protein researchers.

The wet market, housing estate, cinema near his place of residence, and even a few overseas tourist attractions outside the city where Prof. Ma gets recognized by his “fans”. Unfortunately, Prof. Ma can barely recognize the other party at the first glance. He explains that he does not recognize faces very well, but as a doctor, he has at least played his part well enough to be accepted by his patients and their family. In fact, out of the three other units on his building floor where he stays, two of them are inhabited by his patients. Many family members of patients who have passed away still greet him enthusiastically when they see



**Figure 2** Thinking and observation has become two important labels of Prof. Ma.

him, thanking him for his care and effort.

This is Professor Ma, who is described as a “kind soul with a beautiful heart who lives without regrets” in the words of his old classmate.

### Thinking and observation

Coincidentally, in 2006 when Prof. Ma returned from his studies in Hong Kong, the well-known IPASS Research was created. However, he did not know the existence of IPASS back then. In 2004, two American researchers published two articles on the renowned *Science* and *New England Journal of Medicine*, and discovered that EGFR mutation status was related to the curative effects of EGFR kinase inhibitors *in vitro*.

Inspired by these two experiments, Prof. Ma started to look into the clinical applications of EGFR mutation. Prof. Ma had already begun gene sequencing FGFR and EGFR as early as 2001, in the laboratories of HKUST. Back then, they designed the primers themselves, and carried out PCR and sequencing the samples. The detection methods, which greatly paled in comparison with what it is today in terms of sensitivity and accuracy. At that time, the father of Prof. Ma’s advisor in Hong Kong unfortunately contracted lung cancer, and the consumption of targeted drugs was still at a stage where patients took them blindly.

All these conditions motivated Prof. Ma to devote himself to researching the significance of EGFR mutation detection in guiding clinical targeted drug therapy, and have enabled him to lead his team to be the first to do research in this scope in the Jilin Province, as he became one of the pioneers of the field.

From IPASS to AURA3, anti-EGFR targeted drugs have gone through a decade. Prof. Ma habitually asks “why” to the curative effects and resistance of every drug: why do

EGFR-mutated patients react better to Gefitinib? Why are the curative effects better on patients with mutated exons 18 and 20? Why does third-generation EGFR TKI Osimertinib have a higher selectivity to patients with exon 20 T790M mutation...

His work and study in HKUST was primarily to enlighten him on understanding the function mechanisms of drugs. He says that basic research is extremely important to a clinical doctor’s growth. The 4 years have cultivated Prof. Ma’s thinking and observation skills (*Figure 2*). For questions such as: how EGFR TKI drugs advance in generations, the locus where drug resistance is most probable, he habitually explains it using function mechanisms, and hence makes it easier to understand the corresponding treatment methods.

The habit of thinking and observing every matter that comes his way is something Prof. Ma has persisted in doing to this very day. When he was in the midst of putting together the Norman Bethune Thoracic Cancer Multidisciplinary Team, not only did he travel to the Laval University Institute of Cardiology and Pulmonology in Quebec to learn, he also suggested going to where the research team of Professor Shun Lu of Shanghai Chest Hospital was, who at that time was at the forefront of thoracic tumor MDT, and stayed there to observe and learn for more than 2 months. Prof. Lu was allegedly surprised at his suggestion, as his was the first team in China to visit.

### Tenacious and harmonious

MEF2 is an important enhancer in the mobilizing of skeletal muscle cells, and Prof. Ma’s advisor was always hoping to study the modification of acetylated MEF2 factor. Prof. Ma took this mission upon his own hands after arriving in Hong Kong in 2002.

Prof. Ma remembers MEF2 as challenging. He had to wait at least 1 month before finding out the results of a single experiment. This process was tough, as he needed to always prepare himself to start again from scratch if the experiment failed a month down the road.

Moreover, Prof. Ma’s advisor was known for being strict; he believed that even if the results came out to be positive, one should not be self-contented with thoughts of submitting an article immediately, and should instead verify the results repeatedly. “*Arguing the pros and cons, animal testing and practical testing are all required, therefore it takes about 2 years after a positive result to publish in Molecular and Cellular Biology.*”



**Figure 3** Prof. Ma leaving Hong Kong University of Science and Technology (HKUST) in 2005.

But Prof. Ma is gratified, because this research is not only relevant to one as a postdoctoral research topic, but also has great clinical value. Recently, his advisor collaborated with Shenzhen University on a project on amyotrophic lateral sclerosis (ALS), hoping to slow down the rate of amyotrophy by controlling MEF2 and other factors related to the proliferation of muscle cells.

Prof. Ma has experienced dissecting in the dissecting room at temperatures of  $-20^{\circ}\text{C}$ , and even though those memories are bitter, he is certain that it was an invaluable experience, as all other hardships he has experienced seem like nothing compared to what he had to go through then. Not every surgeon has the tenacity to sit on a laboratory bench for 4 years, away from clinic entirely. Even during the SARS outbreak in 2003, Prof. Ma refused to miss a single day, and headed for the lab with a mask every day, even on the eve of the Chinese New Year. Once, he met his mentor and his family by chance, and they were all surprised: you are doing experiments on such an important occasion, Chinese New Year!

7:00 AM, every day, on the grass patch facing the lab, is the time when Prof. Ma is the happiest. He leaves out his precious one hour for his family, and relieves a bit of his homesickness by making long distance calls. 8:00 AM, and Prof. Ma collects his emotions, and is back to the lab with the encouragement and concern from his family.

His hardworking and resilient nature had his advisor keeping him beside year after year. If not for Prof. Ma's son starting school in 2006 and having to return to Changchun to look after him, his mentor would have insisted on him staying (*Figure 3*).

Recounting his times in Hong Kong, Prof. Ma thinks

“merging” was the most difficult part. Firstly, he had to learn how to combine his identity as a clinical physician with his research work, then he had blend in with the Hong Kong locals who were used to only speaking Cantonese, and lastly, he had to mix in with the many foreigners who lived in Hong Kong.

It was time for his test. It was 2004, and one outstanding student representative from each of the three institutions: HKUST, Chinese University of Hong Kong, and the University of Hong Kong was to be chosen to present the fruits of their learning before 160 students from the University of Oxford, the University of Cambridge, and the University of Hong Kong. Aside from the presentation, students also had to accept questions from the floor. Fortunately, Prof. Ma was chosen to be the representative of HKUST due to his outstanding results in the field of MEF2.

In order to not embarrass himself, Prof. Ma prepared for an entire week for the presentation. “*After that, I never get stage fright when presenting a report under any situation. It was because of that experience that I felt like I was reborn, and I feared nothing anymore.*”

### Equality and cooperation

Year 2006, Prof. Ma who had just returned to First Clinical Hospital, Jilin University was called to the director's office. Based on his experience in research, the hospital had hoped for him to make full use of this advantage and move to doing internal medicine. They had wished for him to start taking on work for lung cancer medicine as the hospital was building a cancer center.

“Do whatever is required, and do it as well as possible.” With this motto in mind, Prof. Ma took on the role without hesitation.

Dr. Guojin Liu, who was then the Chief of Thoracic Surgery, was good friend with Dr. Deslauriers, Chief of Thoracic Surgery of the Laval University Institute of Cardiology and Pulmonology in Canada. The hospital invited Dr. Deslauriers, who was a Canadian, just like Norman Bethune, to stay in Changchun for 2 years on a sabbatical, in order to help with the founding of the Norman Bethune Thoracic Cancer Multidisciplinary Team and the Norman Bethune Thoracic Disease Center. Dr. Deslauriers demonstrated international humanitarianism and arrived in China with his partner, putting himself completely into work efforts.

Prof. Ma, along with Hongyan Li, Liping Peng, and



**Figure 4** A photo of Prof. Ma and his advisor in Laval University Institute of Cardiology and Pulmonology in 2008.

Yong Zhao, who were the doctor and nurse representatives of the oncology medicine, thoracic surgery, and respiratory medicine departments respectively, were the first group of key members who were selected to join the multidisciplinary team. In order to be in line with the most recent international MDT ideas, Dr. Deslauriers invited them to the Laval University Institute of Cardiology and Pulmonology to study for half a year.

A doctor was in charge of being Prof. Ma's mentor in the Laval University Institute of Cardiology and Pulmonology. Doing consultations, interacting with patients, seeing patients, seeing every step of cooperation in clinical MDT had become a daily routine for Prof. Ma.

During this time, what Prof. Ma gained the most was a deep understanding of the concept of equality and cooperation (*Figure 4*).

Back in Hong Kong, Prof. Ma understood the great significance of the word "equality" from his advisor. His advisor always gave him an equal chance to interact and communicate, and never compelled him to follow his ways just because he was his mentor. Prof. Ma realised that MDT discussions were similar in the sense of equality, and it felt extremely realistic.

Dr. Deslauriers had two immovable principles. One, patients who required MDT discussions needed to make an appointment, and cannot be added into the discussion at the last minute. Two, all cases are kept confidential from all involved doctors before consultation; doctors are not allowed to prepare by checking up on information. His principles highlighted the importance of discussing matter equally, and having to make decisions spontaneously.

Dr. Deslauriers was naturally the core of the discussions. However authority may be questioned sometimes, as Prof.

Ma stood up to him and said "no" once. A patient who was involved in an MDT consultation had several metastatic tumors. Prof. Ma was of the opinion that there may be pleural metastasis, and that he was not suitable for surgery. Dr. Deslauriers, however, was insistent that patients who have metastatic tumors in their pulmonary lobe may still benefit from surgery. Just as the argument became heated, Dr. Deslauriers asked Prof. Ma angrily: "*Do you know who the first person in the world to write about multiple lung metastases surgery is?*" To that, Prof. Ma calmly replied: "*I don't know.*"

Afterwards, he found out that this person was Dr. Deslauriers himself. His insistence on the case led him to attempt a surgery on the patient, but during the surgery, they found out that the pleura had indeed undergone metastasis, just like Prof. Ma had predicted, and they did not proceed with the procedure. Dr. Deslauriers then approached Prof. Ma, and told him: "*Ma, you were right, and I was wrong.*"

Now, even though Dr. Deslauriers has left Changchun for years, Prof. Ma has kept in contact, and when he returns to Changchun from time to time, Prof. Ma still brings him to have the tofu skewers that he has never seemed to forget about.

The convergence of values is something that Prof. Ma has always emphasized on; he believes it is the foundation of bilateral cooperation, and such is the case with anyone and anything. Dr. Deslauriers had previously shared that any principle should be one where patients are truly at the core, and one where patients can receive the best treatment. He resonates with that strongly.

In the beginnings of the Norman Bethune Thoracic Cancer Multidisciplinary Team, the oncology medicine department had the fewest patients. Despite that, the other departments looked at the big picture, put their patients first, as they selflessly provided great assistance to the oncology medicine department. Especially after the appointment of Dr. Guoguang Shao as the Chief of Thoracic Surgery in 2008, the cooperation between the internal medicine and surgical departments became closer. Consultation frequency changed from weekly to daily, every morning from 8 to 9, and has persisted to be this way for the 9<sup>th</sup> year this year.

Once, when Dr. Gening Jiang from Shanghai Pulmonary Hospital visited the hospital, he was just in time for one of their MDT consultations, and sang praises of the team's insistence on consultation over the many years without a break. He also referred to the team as a role model in the field.



Figure 5 Prof. Ma is proud of his team with high expectation.

### Virtuous and seeking perfection

Prof. Ma is still a strong follower of the Norman Bethune philosophy. He says that the hospital's motto is "Virtues of a Great Physician", which he believes is a further interpretation of the Norman Bethune philosophy. Selflessness, contribution, international humanitarianism—these traits seem to boil themselves down into the words of the motto.

Virtue is the purification of one's soul. Virtue to Prof. Ma is to sacrifice yourself for the greater good, and patients should always come first in every matter.

Seeking perfection is to make sure that one's doing the best that they can. Prof. Ma thinks that seeking perfection is the bare minimum for a doctor. If one can't do that, it would be impossible to do anything.

Changchun is not a big city, but it is not exactly small, either. The permanent population in the urban area is close to 5 million. Prof. Ma who has almost never been to the wet market before, went there with his wife for groceries once. When he reached a broccoli store, the owner spoke excitedly: "You must be Prof. Ma. My mother was one of your patients, and while she's no longer here, your treatment plans for her helped relieve a lot of her pain, and the time she spent with us was a lot longer than what we had expected; I really wanted to thank you in person." Finally, she insisted on him taking a broccoli without charge, and he could not refuse no matter how hard he tried. As he carried the broccoli home, Prof. Ma thought to himself: he could no longer come to the wet market.

Not long after, Prof. Ma brought his son to the cinema. A man who also brought his child to watch a movie recognized him: "Prof. Ma, do you remember me? My father was your patient, and your treatment for him back then was..." Prof. Ma could no longer go to the cinema, too.

Prof. Ma who is often busy with work rarely has time to go on a trip with his family. Two years ago, he went on

a trip with them and was taking shelter from the rain on an island, and even then, he was recognized by the family of one of his patients. He could not believe he could even meet them there.

Prof. Ma who wishes to keep a low profile does not think being recognized by his patients or their family is something worth a sense of achievement, in fact, he feels a little embarrassed whenever it happens, because he thinks it is his job to treat his patients anyway.

### Understand history and be upright

When talking about his hopes for the younger generation, Prof. Ma gave it a little bit of thought, and said: "I hope they can read up on history." (Figure 5) After reading on history, they will slowly realise that everything has its own pattern of development, and the more we read up on history, the clearer our understanding on life and work, and history changes one's judgement. "When one understands history, they have their own beliefs, and will have things that they insist on."

An upright person is how Prof. Ma would like other people to see him as. He grew up at the foot of White Mountain, and will hike to the summit at the company of his old classmates by the northern slope (Figure 6). During his hike in 2016, he received a poem made specially for him, describing him:

*I will always remain kind and without regrets.*

*I've always believed, that a beautiful soul makes the world beautiful.*

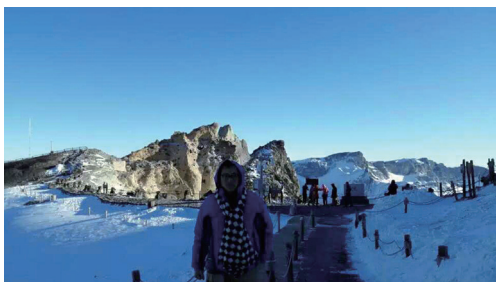
### Conversation with Kewei Ma

**AME:** When you took the lead in starting EGFR genetic detection tests in Jilin, were the patients and their family accepting of the additional costs of detection tests on top of targeted drugs that are already a little costlier than normal drugs?

**Prof. Ma:** It was a detection testing that started in 2006 and an experimental testing of patients' samples, it hadn't reached the stage of clinical-guided drug usage yet.

**AME:** Was the transition from clinical experimental testing to clinical-guided drug testing smooth?

**Prof. Ma:** To be honest with you, it wasn't all that smooth. In the early stages, not even the pharmaceutical



**Figure 6** A photo taken in 2015 when Prof. Ma was climbing at the northern slope of White Mountain.

companies wanted to proceed with it, needless to say, the patients would be even less likely to agree to it. That was because after the detection tests, the population of drug usage needed to be narrowed down, and the companies' profits will be affected. But as research evidence started to accumulate, all parties started to understand more about treatment ideologies, and believed in putting patients first, therefore finding out ways to improve treatment methods became a common goal.

**AME:** *Can you give us an example where the research of drug function mechanisms is extremely beneficial to understanding drug treatment strategies?*

**Ma:** We all know that EGFR mutation normally refers to the mutation of the exons 18 and 20. The mutation of those two exons may increase the sensitivity of EGFR inhibitors, yet the mutation of exon 20 will result in primary resistance of the EGFR inhibitors, or what is known as T790M mutation. Therefore, the succeeding second and third generation EGFR TKI must have been developed with a focus on the drug resistant mutation. This means that drugs had new spatial structure designs focused on this mutation, and out of these drugs, the third generation TKI is more ideal in terms of spatial structure control as compared to the second generation.

Besides, why does drug resistance appear in third generation EGFR TKI? The irreversible goal of Osimertinib is to change the ionic bonds in the c797 locus to a more stable covalent bond. However, tumor cells are too clever; they will change the amino acid mutation in c797 to s in order to resist the covalent bonds, and the drug becomes resistant to the drug. This is also why researchers were quick to locate the locus where third generation EGFR TKI is resistant, and

have already begun research on how to tackle the drug resistant problem.

**AME:** *What sort of impact does your time studying in Hong Kong have on your understanding of research into the future?*

**Ma:** What I felt strongly was that: if there is a conducive research environment for one to concentrate and devote oneself to research without any distractions, nothing is unachievable. If one puts in effort and is steadfast in their work, there will definitely be results.

**AME:** *Why do you think your research on MEF2 could have been published on MCB and JCB? And why would it have been cited close to 50 times?*

**Ma:** Firstly, authenticity. If the research is not authentic enough, it will not withstand the test of time. Secondly, importance. Because its application scope was wide, many researches relevant to skeletal muscles would have been involved. So even if an article may be quite minor, it may be widely cited if there is some sort of universality in the research scope.

**AME:** *Why were you able to stay in Hong Kong year after year?*

**Ma:** I didn't dare to delay all the experiments that I was in charge of. Back then I did four or five experiments concurrently, and as I was waiting on the results of one, I would be working on another. It would have been irresponsible of me to not complete all the experiments I had accepted. Besides, my advisor taught me so much, and I couldn't let him down. Furthermore, when I was in my third year in the lab, I was the one whose skills were the most comprehensive as I had pretty much completed all the relevant experiments in the lab. When newbies join the lab, I have the obligation and responsibility to train and teach them. If I had just upped and left, many conditions of the experiments would have required re-navigation. I couldn't just think of myself and not the lab, or my advisor.

**AME:** *Why did Dr. Deslauriers insist on his two principles?*

**Ma:** He believed that a prior appointment was the most basic respect for a physician. Furthermore, it is only with an appointment can the staff have time to properly prepare

the patient's test results and details, and if they were to be added in last minute, the information would be incomplete, and it would affect the outcome of the live discussion. At the same time, his request for doctors to not look at the patients' details before the MDT meeting is because he hopes everyone can have a spontaneous brainstorm, which is the essence of an MDT.

**AME:** *Why do you keep emphasizing on the convergence of values?*

**Prof. Ma:** This is extremely important. For example, we have worked with Dr. Guoguang Shao for close to a decade, and if we don't share even the most basic values, there would be no cooperation to speak of. When you meet a partner who shares your values, any obstacle you face is not a big problem as long as you work together and remain determined—other factors are not considered big issues in the face of one's core values.

**AME:** *If you don't feel a sense of achievement from being recognized by patients and their family, what exactly gives you a sense of achievement?*

**Prof. Ma:** Patients that I've seen over many years who come in for a review after many years. I feel the happiest, and the greatest sense of achievement when they walk in to see me.

**AME:** *What is a memorable gift you have received recently from a patient?*

**Prof. Ma:** There is an old lady who doesn't do very well

financially at home, but every time she comes to see me, she insists on giving me something before she leaves, and wouldn't take no for an answer. During her most recent session, she told me: "Prof. Ma, look, my family is not well to do, and I didn't bring much, so I thought about it for a long time, and thought about how difficult it must have been on you to do your consultations, why not I gift you this lumbar physio device?" And she didn't wait for me to respond and put it on me. The device was warm and released heat, so I wear it out to do my consultations.

**AME:** *Going back to 2002, before studying at HKUST, what would you like to say to your 2002 self?*

**Prof. Ma:** Your hard work and efforts will not go to waste. Hang on tight.

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### Footnote

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