The Adventures of

By The Centre for Applied Genomics

CHAPTER 1

Our story begins one late evening on the fourteenth floor of the MaRS Centre East Tower. Steve Scherer was just about to start reading a paper that one of his post-docs had written, when he heard a loud clatter.

"That's strange…", he thought to himself, for no one kept the odd hours he did and he had thought that the floor was deserted. He peeked outside his office and, surely enough, he found it abandoned. Yet the noise continued.

"Clang! Clang! Clang!"

His curiosity got the best of him and he decided to find the source of this odd metallic rattle.

"I guess that Kohji's paper can wait till tomorrow. He's waited two months already, one more day won't hurt."

He followed the noise down the hallway…

"CLANG! CLANG! CLANG!"

…and he noticed that it was coming from the common equipment room. When he stepped inside, he saw an ultracentrifuge shaking dangerously.

"Grad students!" he grumbled. "They can't even balance an ultracentrifuge!" But, as he approached the machine to turn it off, its movements became more and more erratic. Just as his finger was about to touch the button, the machine spun out of control!

The next morning, Jennifer entered the lab and noticed that the lights in the office were still on.

"That's strange…", she thought, since she was usually the first person to arrive in the morning. Then, to her utmost surprise, she heard screams for help and they seemed to be coming from the common equipment room!


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Jen ran as fast as she could, and there she saw Steve lying underneath an ultracentrifuge machine. Jennifer quickly followed the emergency protocols that had been clearly outlined by Occupational Health in the countless meetings that she had attended. The paramedics arrived and carried Steve to Toronto General Hospital. Everyone in the lab waited anxiously for word on his condition, and a few hours later, Jo-Anne came with news.

"Well," she started, "the good news is that he's OK. The doctors have said that he hasn't suffered any life-threatening injuries." An audible sigh was heard, as everyone let out a breath of relief.

"But," she continued, "the problem is that... well... he's flat."

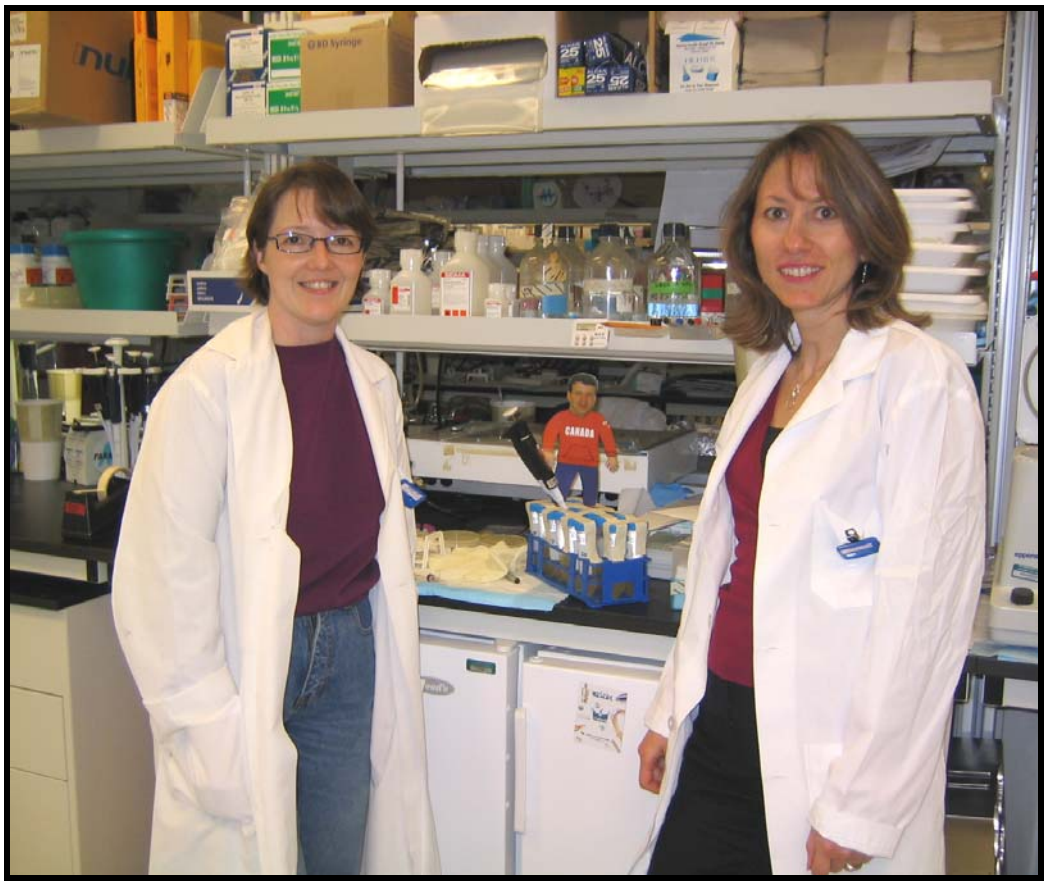
"What do you mean, 'he's flat'??", everyone asked in unison.

"Well, the doctor's have said that, strangely enough, he's been flattened."

“You mean, like a pancake?” asked Sanjeev.

“Or a leaf?” asked Barbara.

“Or a paper?” asked Beverly.



“Yes, yes, and yes,” replied Jo-Anne. “It’s the first time that doctors have seen anything like this.”

“So, when will he be back?” asked Andrew Du.

“Well… You know Steve… Since he hasn’t suffered any major injuries at all, unless you consider flatness an injury, he wants to come back to work tomorrow.”

“WHAT??!!”, yelled everyone in disbelief.

“I know!” said Jo-Anne. “I’ve told him to take some time off so that he can adapt to his new condition, but he said that OGI reports are due soon.”

Meanwhile, in a ward in Toronto General, Steve was pondering the many events that had taken place. His mind was whirring at a million miles a minute. Why had he become flat? Was there a scientific reason for it? Everything that he had ever learned told him that last night's events should have led to serious injuries, even death. But there he was, flat as a paper, still kicking.

Then and there, he decided that he'd do everything he could to find a cause for flatness, and maybe somewhere along the way, he'd figure out how to become normal again.

CHAPTER 2

When Steve came into the lab the next day, he called for a meeting. He explained his ideas to the lab, while they all looked at him inquisitively. Kamala went one step further and kept walking around him in circles, completely mesmerized by the flatness of the person in front of her. Indeed, none of them had ever seen a flat person, much less a flat PI.

Steve ignored everyone's curious looks and tried to address the crowd. But it proved to be much more difficult than he expected, since anyone looking at him at a 90º angle couldn't see him.

"I'm going to apply for funding," he said, "and I'm going to submit an application to the Ontario Provincial Government. If we get turned down, I think that CIHR would give us the grant for this project. In the meantime, I want you to start thinking about ways to find genes causing or associated with flatness."

Steve prepared to plea his case at Queen's Park while everyone else went to work and scrambled to get the CIHR grant together in time. As expected, he was turned down by the Ontario government. The politicians had felt that there wasn't enough public interest in finding genes associated with flatness, since it affected such a small fraction of the population. Besides, he didn't have any of the required co-funds either. Steve returned to the lab exhausted, but still had hopes of receiving a CIHR grant.

Jo-Anne, Jennifer, Emiko and Julie struggled to put together all the costs and estimates for the grant, while all the members of the academic lab made figures and wrote paragraphs about finding flat genes. Steve corrected, wrote, and edited all the drafts with his famous wrathful red pen (which he had no difficulty gripping despite his flatness). Finally, the

grant was submitted and everyone had high hopes of its acceptance. Then, the long wait began for the announcement of winners.

But Steve couldn't wait. He decided to begin the project, and his first step was to find out whether other flat people existed. If he could find a large enough population of "flatties" (as he was calling them), maybe he could find linkage to a gene. First, he visited his parents to see if anyone in his family had ever become flat.

Steve's mother couldn't recall any flat relatives. Neither could his father. Both of them remembered occasions when they had stubbed a toe or gotten trampled on. They had only gotten bruises and bumps, never flatness. Steve figured that it wasn't caused by a dominant gene. Jo-Anne clearly recalled a day when Josef's finger had gotten squished in a cabinet door. So he wasn't affected either.

He decided to call all the clinicians that he knew and began by calling Dr Wendy Roberts at Sick Kids Hospital. He told her that he was looking for flat patients.

"Do you mean malnourished?" she asked.

"No, I mean flat", replied Steve.

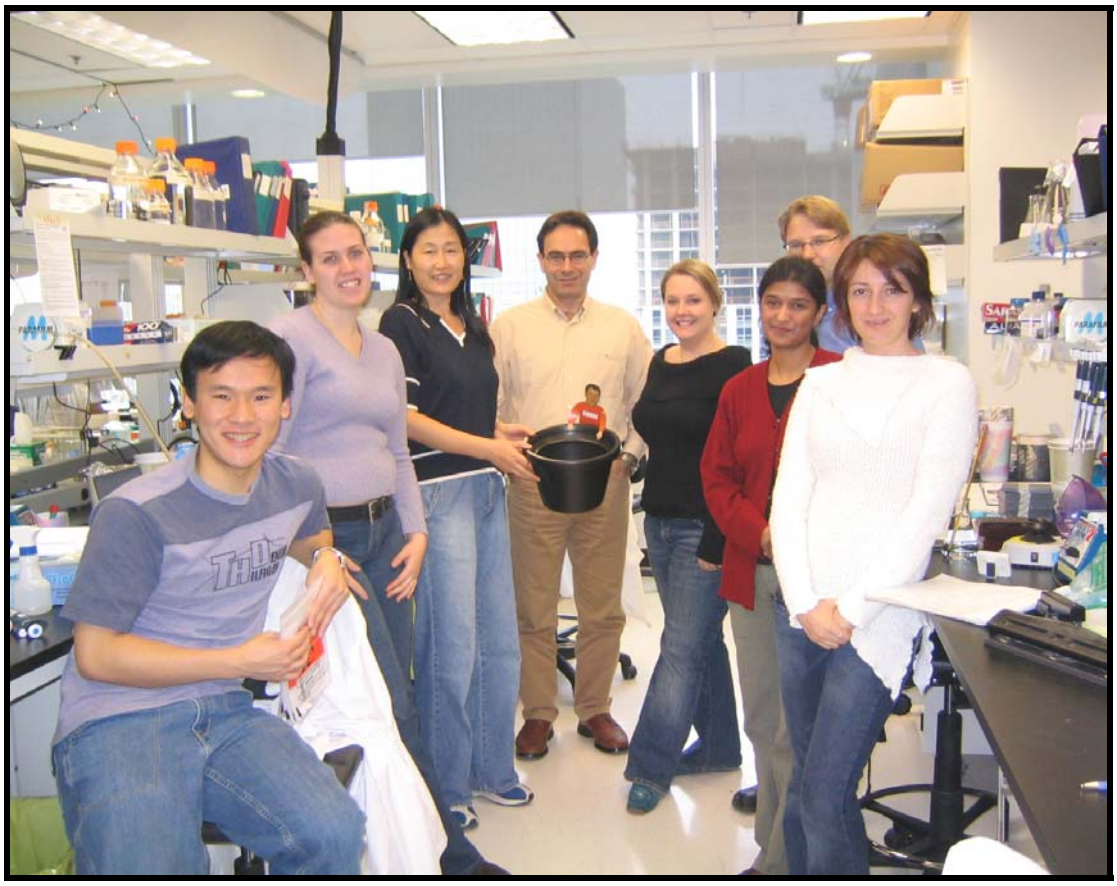
"Underweight?" she asked again.

"No. Flat. As in two-dimensional. Like a plasma-TV. Or a flapjack. Or a- "

"OK. I'm getting the picture. Flat. No... I've never treated anyone with those symptoms. Sorry!"

He called countless doctors and had the exact same conversation with every one of them. None of them had ever treated a patient with the phenotype that Steve described. He was about to give up, when he called Dr Berge Minassian.

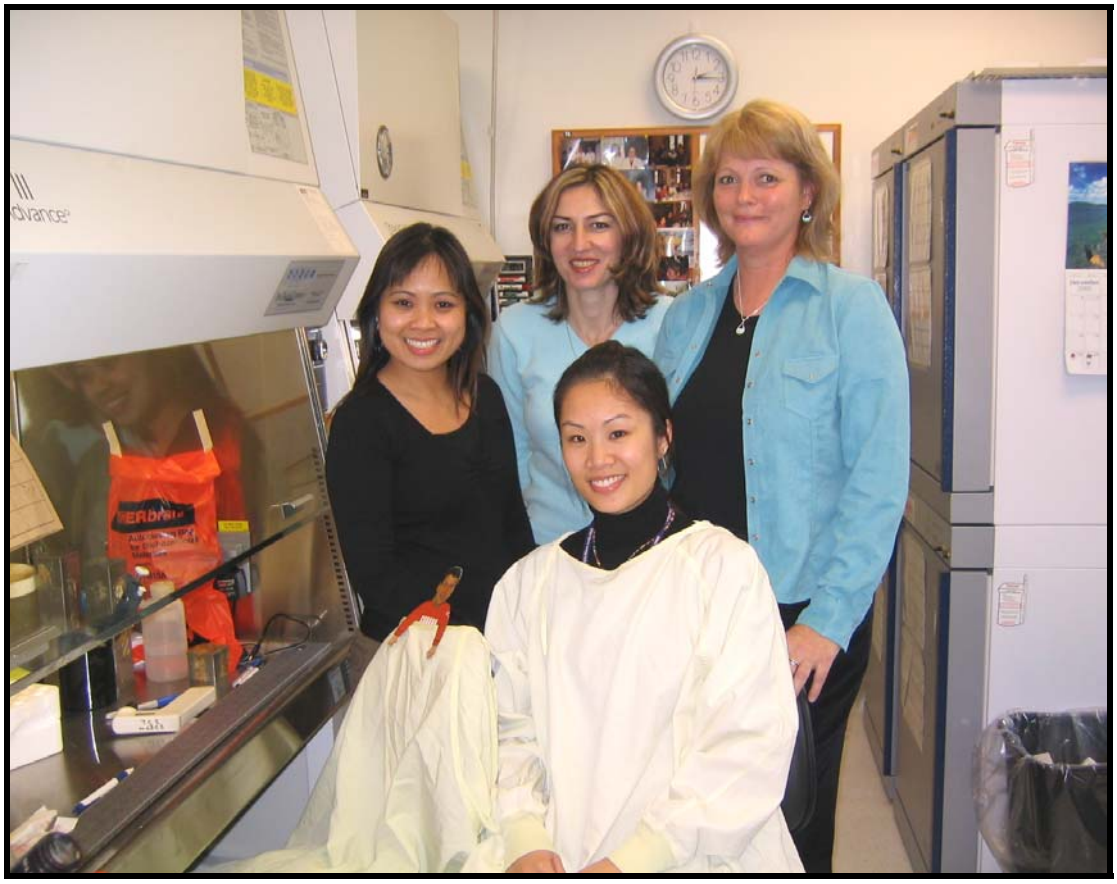
"Actually," said Berge after Steve described his quest, "I've never had a flat patient. BUT, I've heard of some dogs that don't die when they get run over. Instead, they become flat. They're being bred since they make better pets for children. No one wants a dog that can become road kill, right? I'll talk to the breeders to see if I can get some DNA or blood from a tail clipping for you."



When Steve hung up, he was ecstatic. He couldn't believe his luck! And just then, he received an e-mail: his grant had been awarded.

CHAPTER 3

The dog blood finally arrived and Laura rushed to deliver them to the cell culture facility. Staff and technicians went to work, trying to establish cell-lines for the precious samples that had arrived. Nancy checked on them everyday to make sure that they were growing appropriately. One day, as she looked through her microscope, she noticed something odd about them. She looked at them at a higher magnification and they still looked strange. She called all the staff and, one-by-one, they each took turns looking at the cells.



"They *do* look strange", said Jingle.

"They look... How should I describe it...?" wondered Charlene.

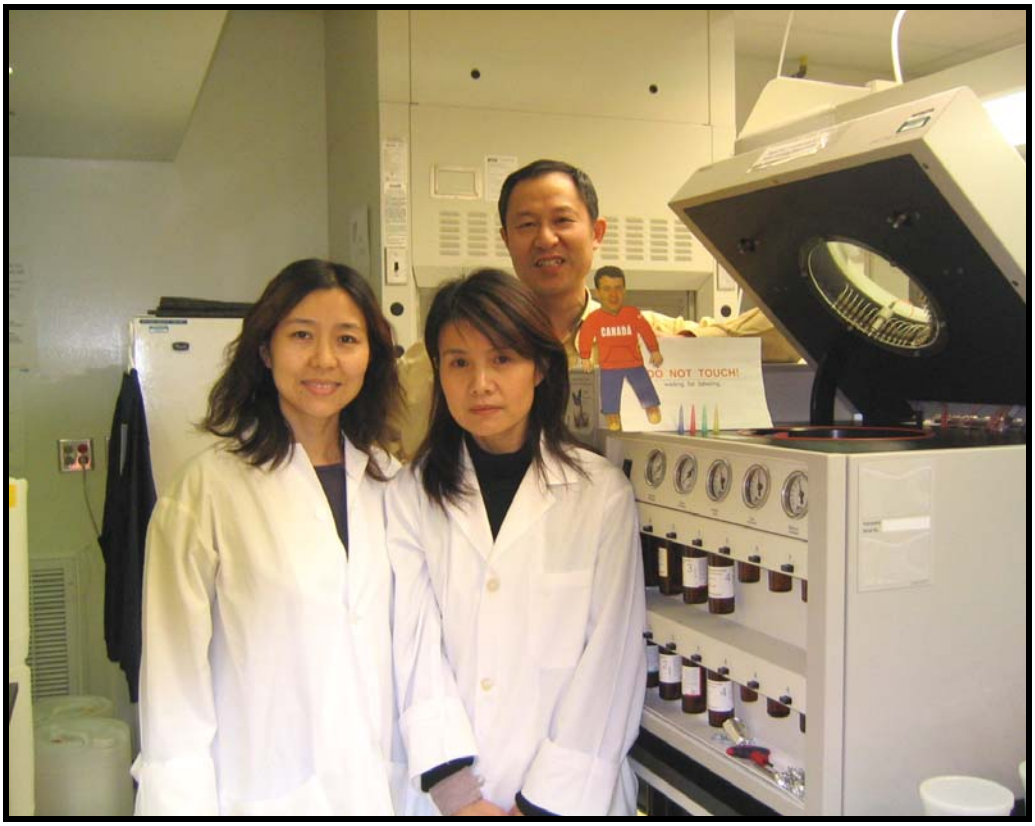
"I guess you could say that they look a bit flatter than usual" said Anca.

"Like a pancake" finished Tomoko.

And although the cells had pancake-like features, they grew normally. Finally, Dr Peter Ray's molecular diagnostic laboratory extracted DNA and passed on to the genotyping facility at TCAG.

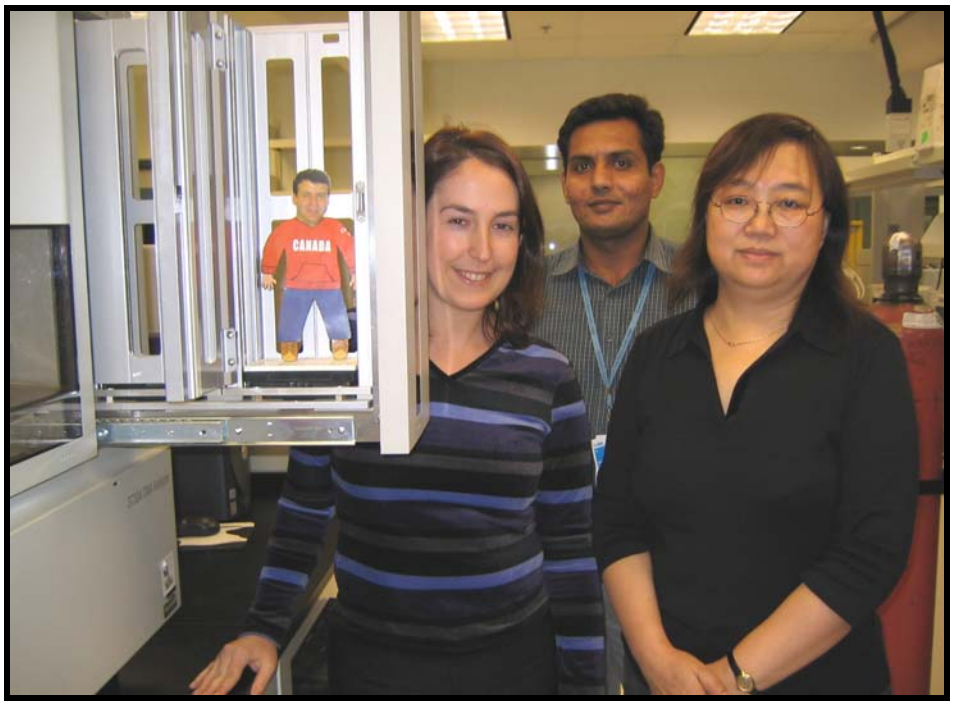
CHAPTER 4

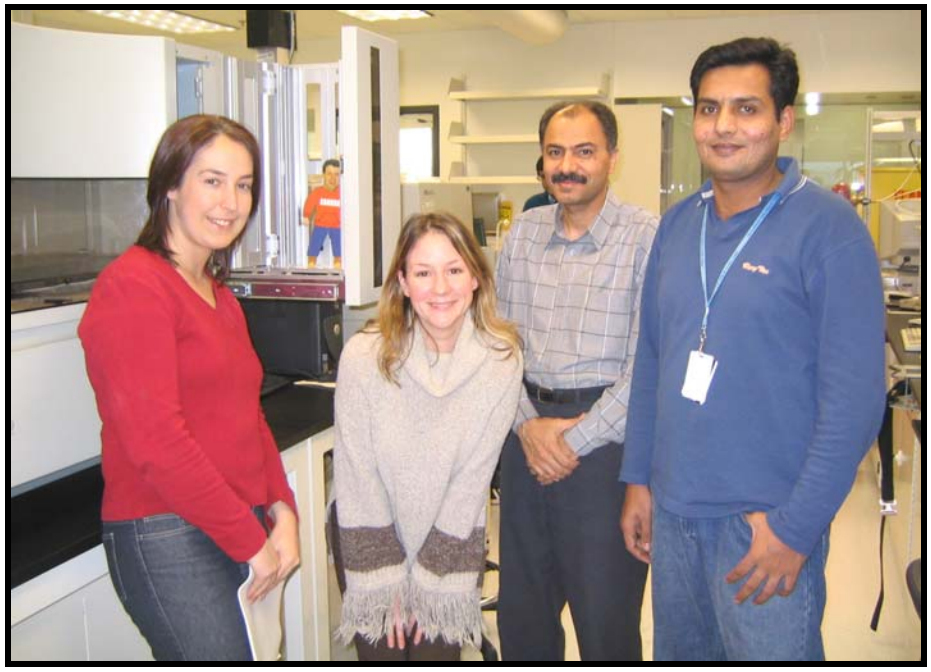
The genotyping facility at TCAG went to work. Tara designed additional markers throughout the dog genome for the linkage analysis. Simone ordered primers using the new online system, which Junjun insisted everyone had to use. Zhizhou and Patricia went to work preparing and purifying them. Everyone at TCAG knew that this project had utmost priority and they worked around the clock, 7 days a week in order to complete their tasks.



Once the primers were ready, Jane rushed them across the bay to the genotyping facility. Abdul, Jean, and Ali performed the PCRs for the markers. Everyone had high hopes of finding a single locus associated with flatness. The results were send to Andrew Paterson for analysis, but when the results came in, no single locus stood out as having a strong LOD score.

"I guess we're back to square one," said Tara. "I'll have to go tell Steve the news." But Steve hadn't had expected any miracles and had planned for this. He suggested that they send to the dog cells to the FISH facility for karyotyping.





CHAPTER 5

Martin called all members of the FISH facility for a meeting. "We need to look for any major karyotypic differences in the dog DNA. But we might have some trouble since the cells are slightly flat."

"Do you mean flat as in unhealthy?" asked Mark.

"I think he means oblong" said Sherilyn.

"No. I've seen these cells. They're flat. Like a board" said Ciara.

"This is nonsense!" said Ann, "I've worked with mice cells, and chimp cells, and gorilla cells, and they've been difficult enough. Flat cells are a recipe for insanity." Vikram agreed with Ann's statement, muttering "flatness is madness" under his breath.

"Well, we'll have to see if we can get them to work," said Yongshu.

And that's just what they did. They fussed and stressed, just as FISH people do, but sure enough, they got beautiful karyotype pictures. Yet their findings didn't indicate any major chromosomal rearrangements.

"I guess we'll have to tell Steve the news," said Ying. Again, Steve hadn't held his breath for any breakthroughs with FISH. "We'll just have to try something else. Maybe we can do a microarray comparing dog expression with flat dog expression. Who knows what we can find?"

CHAPTER 6

"Microarray with dog RNA? What kind of chip are you planning to use for that?" asked Chao, when the idea was proposed to him.

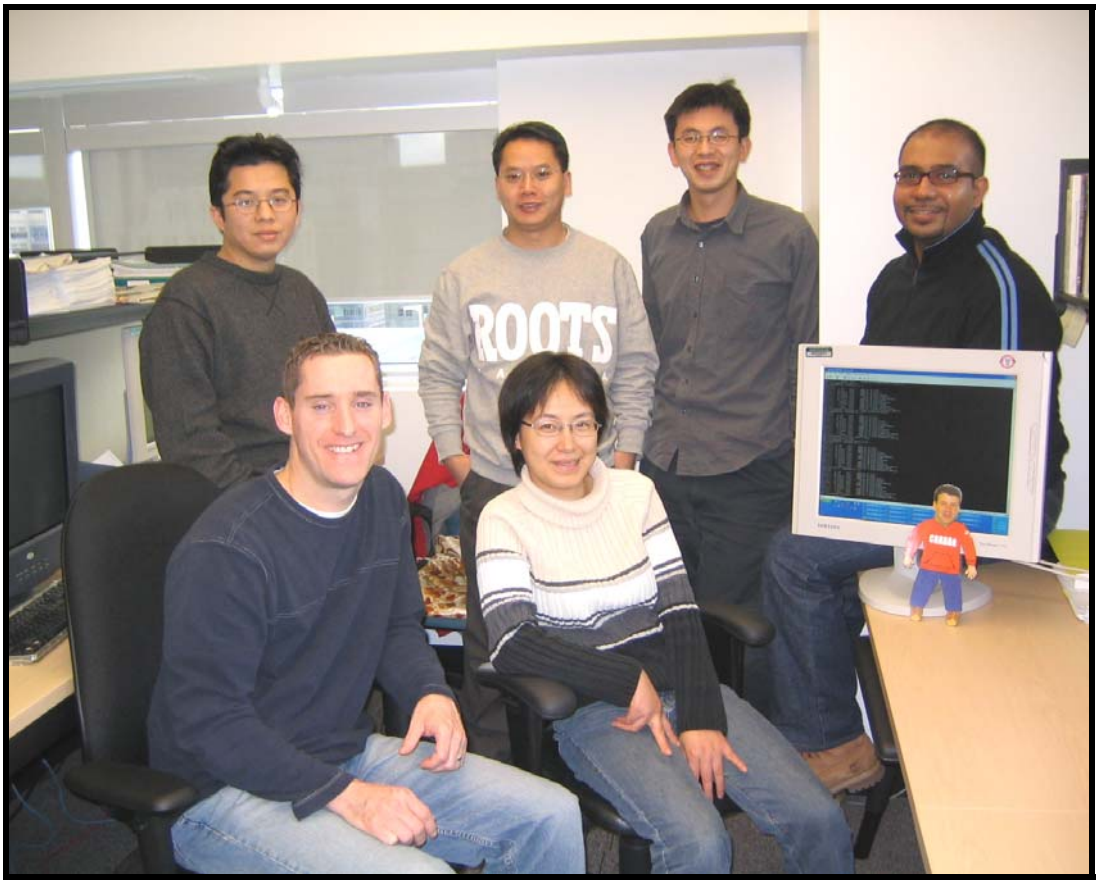
"Well, maybe we can design a chip with dog oligos on it," suggested John.

"I agree. We already have experience designing chips, don't we? We designed one for the chromosome 7 exons," said Razi.

"Yeah. And we all know how amazingly successful THAT was," laughed Jeff.

"Why don't we just use Steve's RNA on an Affy Chip?" suggested Osa.

"That's a good idea!" said Cheng.



But this proved to be a much more difficult task than expected. When Steve went to have his blood drawn, the needle couldn't be inserted anywhere. Of course, the doctor's were afraid of poking a hole straight through him! And although Lan and Xiaolin suggested that they simply cut Steve with a pair of scissors, the microarray experiments were eventually abandoned.

CHAPTER 7

Steve e-mailed his academic lab: "OK... I'm paying you guys the big bucks. Let's see if you're worth it. How are we going to find this thing?"

The academic lab quickly got together for a meeting, for there is nothing that post-docs and grad students enjoy more than lab meetings, especially when timbits or cookies are present. As usual, Lars presided over the meeting and started by saying:

"Well, maybe there's a copy number variant associated with flatness," he suggested, "perhaps there's some sort of duplication. I think we ought to perform array CGH."

"But remember that we don't have any blood from Steve," said Yan.

"True... True..." he replied.

“Hmmm… But we don’t actually need blood, do we? We could simply use DNA from another source” said Makiko.

Andrew said, “His hair is still normal, isn’t it? If we pulled enough of his hairs out, we could get enough DNA. The doctor’s couldn’t get his blood because he was flat, but nothing has really happened to his hair.”

“That’s the dumbest idea I’ve ever heard,” said Layla, “we could just get DNA from a swab.”

“Well… YOU’RE a dumb idea!” Andrew retorted intelligently.

And while the two grad students fought in the background, the post-docs continued brainstorming. Indeed, the post-docs had learned to ignore the constant bickering of the yet-to-be-doctors. Finally, Dorota spoke up with an idea: “I personally think that we should be looking into the neurological aspect of Steve’s condition. How come he didn’t feel any pain when the ultracentrifuge hit him? How can these dogs simply get up and walk away after being hit by a car? Those are the questions that we should be asking!”

Yan said, “I think we should focus on the fact that his hair is normal. It maintained its natural shape, so we should be looking at genes expressed in hair follicles and see how they’re different. Perhaps we should start by looking at C7orf11.”

“Well, I think we should look at the pattern of inheritance,” argued Shin-ichi. “The fact that flatness isn’t present amongst Steve’s relatives suggests a complex pattern of inheritance. Perhaps the gene is imprinted.”

“I’m sticking to my original theory. I think that array CGH is the way to go” retorted Lars.

“How many times do I have to repeat myself?! Neurological studies!” yelled Dorota.

“Im-print-ing! Im-print-ing! Im-print-ing” sang Shin-ichi. Layla and Makiko joined in the chants.

The conference room had turned into a circus ring. Yan was trying to voice her theories, but no one would listen. In an attempt to get Shin-ichi’s attention, she pelted him with a timbit and suddenly there were timbits flying everywhere! Christian was so aghast at the total lack of respect towards this Canadian icon that he stood up on the table shrieking “Stop the madness! Someone, please stop the madness!!!”

At that very instant, the conference room door opened and Steve walked in. Timbits were strewn everywhere. Dorota’s hair was covered in coffee that Kohji had dumped on her. Layla was hiding under the table, still muttering “imprinting”. Steve looked around in utter disgust. After a long, painful silence he said, “Well… I’m guessing that you don’t have anything to report.” And with that, he left the academic lab in a sea of wasted, sweet deliciousness.

Steve went back to his office writhing in anger. What was he to do now? TCAG had no results and the academic lab was definitely useless. Who could he turn to? At that moment, he looked around his office. His eyes were drawn to the many publications that he had framed and he suddenly had an idea. He could ask his former collaborators for help! They were some of the most brilliant researchers in the world. If there was anyone who could make him normal again, it would be one of them.

CHAPTER 8

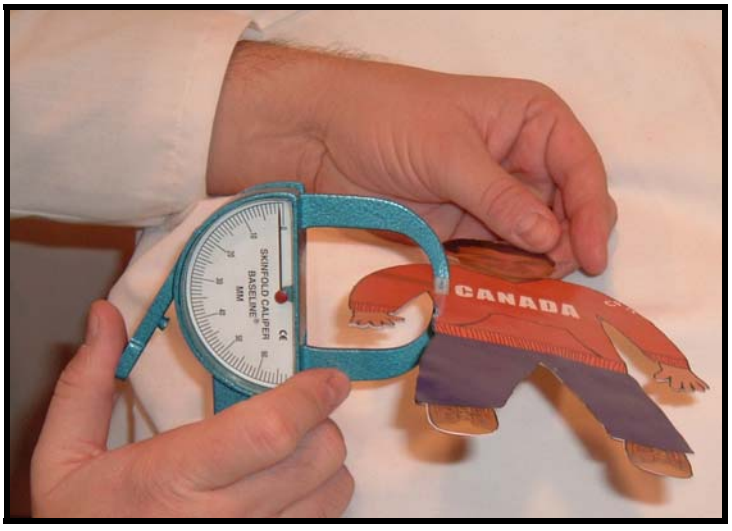
He began by visiting Dr Lucy Osborne at the University of Toronto. Lucy had heard about Steve's flatness from Dr Jeffrey Lee, so she was aware of his condition as she met him in the lobby of the Medical Sciences building. Steve thought that it was strange that she would come down to greet him. He had met with her countless times in the building, and they always met upstairs. Secretly, Lucy was scared that Steve might fall down the elevator shaft by slipping through the cracks, so she had preferred to meet him on ground floor.

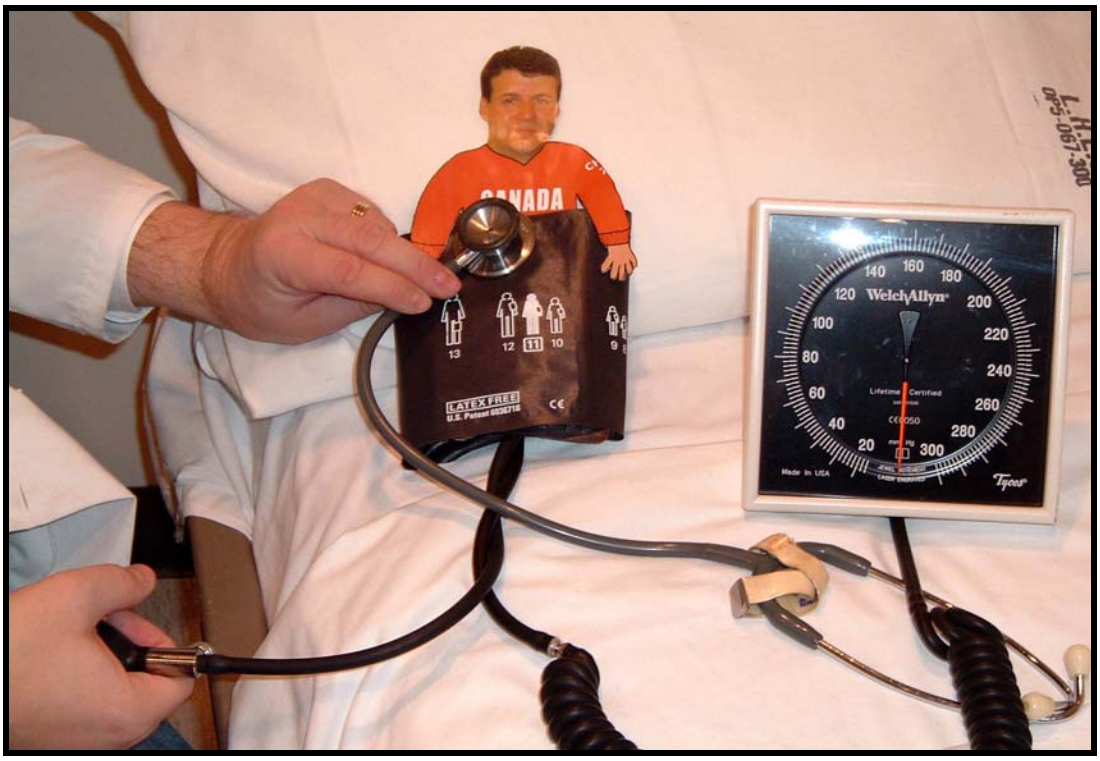
After explaining the reason for his visit, Lucy told him, "Well, none of your symptoms overlap with those seen in WBS patients. So there isn't much that I can do for you. I'll keep thinking about it, though." And with those words, she left Steve with his growing despair.


CANADA

CHAPTER 9

Next, he visited Dr Rob Hegele at the Robarts Research Institute in London, Ontario. Dr Hegele was also a medical doctor, so he was quite intrigued by Steve's condition. He gave Steve a full examination, measuring his height, weight, and width. But nothing prepared him for what he saw when he took Steve's blood pressure. It went through the roof!! He measured his pressure again, and again, and every time he got the same extraordinary readings. Dr Hegele thought that since Steve hadn't lost any blood in his accident, yet his veins had become flattened, there was increased blood pressure in his system.





So, he suggested that they look into the vascular aspect of his flatness. He hypothesized that increased elasticity of blood vessels may have helped in the flattening of Steve's organs.

He took a sample of Steve's DNA from spit and he set his lab to work to find a possible *de novo* mutation in genes known to play a role in vasoconstriction or vascular elasticity. After several days of hard work, mostly done by the arduous labour of graduate and co-op students, they had no results. Dr Hegele called Steve into his office:

"Steve, I hate to break this to you, but we ended up with nothing" he said.

Steve's shoulders slumped at this news. "Well, it's not your fault. I guess I'll have to keep trying."

Dr Hegele looked at Steve with a gleam in his eyes and said, "You know, I've been wanting to ask you this, but I didn't know how to bring it up. Since you're here, would you mind doing rounds with me? I've spoken about you to my medical students and they're fascinated. They'd like to examine you."

Steve shuddered at the thought of being prodded and poked at by dozens of eager medical students and said, “Well, Jo-Anne’s expecting me back in Toronto. I’ve got to run!” And with that, he fled as fast as his flat feet could carry him!

CHAPTER 10

His next trip took him to Ottawa, where he met with Dr Dennis Bulman at the Ottawa Health Research Institute. Dr Bulman had actually seen Steve on television, on an in-depth analysis the CBC had done on him entitled "Genes in 2mm Jeans". He had waited eagerly to meet and talk to Steve.

"So Dennis, what do you think I should do?" asked Steve, after they had sat down and chatted for a few minutes.

Dr Bulman stared intently at Steve. Suddenly, without any warning, he reached over and punched Steve in the stomach! Steve buckled over and started screaming out in pain.

"What the hell did you do that for?" yelled Steve.

"I think it's odd that you survived this accident and I wanted to see if you could still feel intense levels of pain," replied Dr Bulman.

"Couldn't you have just asked me that?" asked Steve, still red in the face from the pain.

"I wanted to ensure that you could sense sudden, unanticipated pain. We'll have to think of something else, then," explained Dr Bulman.

He suggested that they look into genes known to play a role in indifference to pain, and that they use the DNA from the dogs for this analysis since there were more samples to look at. Over the next few days, his entire lab worked on this new project. Steve went had nothing to do but wait, so he went on several walks and even went to visit his old lab at 100 Sussex Drive. But eventually we couldn't sit idly around any longer. So Steve came out of "laboratory retirement" to help speed up the experimental process. Dr Bulman couldn't help but laugh at Steve when his first PCRs were contaminated.

The members of Dr Bulman's lab seemed oddly clumsy to Steve. One of them dropped a water bottle on Steve's foot, another one accidentally cut Steve's hand with a blade, and yet another one rammed a cart into him. Steve finally spoke out when one of the technicians "mistakenly" spilt a few drops of HCl on Steve's chair, which he then sat in.

As Steve entered Dr Bulman's office, Dr Bulman looked up and said "Ah, Steve! I was just coming to see you. Please, have a seat."

Steve sat down and said, "Listen Dennis, I've got to talk to you about your staff-"

"Wait!," interrupted Dr Bulman. "I've got to say something first. We got the results back from the sequencing analyses. Nothing… There are no mutations in the dogs. I'm sorry."

Steve fell silent. Dr Bulman continued. “I’m really sorry about this. Anyway, what is it you wanted to tell me?”

Steve looked up, “Huh? Yes… Right… Your staff. They seem really clumsy. It’s actually quite dangerous. You should think about getting new students. Even my students seem like Nobel laureates compared to yours.”

Dr Bulman shifted uncomfortably in his seat and his eyes avoided Steve’s, “Yes… Um… I’ll have a talk with them. I don’t know what’s gotten into them recently…”

Steve stared at Dr Bulman and said, “Did you *ask* them to hurt me?”

“Wha- What?!?! Of course not! Anyway, you should get going. Jo-Anne just called me to make sure you were going back to Toronto today. Yes! It was nice working with you! Bye!”

And with that, Dr Bulman pushed Steve out of his lab, leaving him wondering what to do next.

CHAPTER 11

Steve was stressed and felt as though he were running out of options. He locked himself in his office and read papers day and night, searching for a description of a flat patient or a clue as to what he should do next. He didn't eat, he didn't sleep, and he wore his lab coat to keep himself warm.

One late night, he received a phone call from Johanna Rommens. She had heard about his hours in the office and had grown concerned for his physical and mental wellbeing. She suggested that he speak to a psychologist to deal with the stresses he was enduring. Steve considered this a waste of time, but he eventually promised to call a professional after Johanna spent an hour trying to convince him to do so.

He called Dr. Peter Szatmari at McMaster University. They had spent countless hours on the Autism project, and Steve felt that he could confide in him.

“Peter, I hate being so flat. I don’t know what to do.”

Peter replied saying, “Well Steve, you might be long winded sometimes, but I wouldn’t say that you’re dull or boring. What makes you think you are?”

“No! That’s not what I meant. I mean flat, like a penny. Or a movie screen.” Dr Szatmari was suddenly alarmed and thought that Steve had lost his mind. Steve had to describe his saga in order to convince him otherwise. Peter thought about the dilemma that Steve was in and decided that the best thing to do was to give him even the slightest shred of hope.

"Listen Steve, you still have tons of options. You haven't even spoken to any of your collaborators abroad. Why don't you do that?"

Steve marvelled at the wisdom of his sage friend, and silently thanked Johanna Rommens for wrestling with him for an hour on the phone.

CHAPTER 12

Steve decided to follow Dr Szatmari's advice. He started prepare a trip to visit several of his collaborators abroad to consult with them about his condition. But preparing for the flight was an ordeal unto itself. Due to the amount of press coverage that he was getting, Steve was gaining recognition worldwide, even by government officials. The American government had issued a statement saying that Steve posed a threat to national security, due to his ability to gain access to restricted areas. They had proposed several hypothetical scenarios, where Steve could be mailed in an envelop to the White House and assassinate the Bush administration's scientific advisor or slip under doors of the CIA and steal national secrets. Consequently, Steve's travelling arrangements were being scrutinized. He only managed to briefly visit Elayne at Harvard and Joe in Vermont before the American government banned him from further entries. These visits were so brief that he barely managed to tell them his story before having to catch his flights home.

Finally, his itinerary to Europe and Asia was ready. His first stop was in Germany, where he planned to meet with Drs Konstanze and Hartmut Döhner at the University of Ulm. After an exhausting flight to Europe, he arrived at Ulm and went to the University straight away to meet with them.

Although they had suggested that Steve rest for a while, he was in quite a rush and too eager to talk to them.

After the initial shock of seeing Steve, the Drs Döhner went to work. After hours of research and discussion with the members of their lab, they approached Steve with their answer.

Hartmut started off saying, “Well Steve, as you know, our area of expertise is acute myeloid leukemia. And there isn’t much similarity between leukemia and flatness.”

“For any experiments that we’d like to perform, we need your blood, and we understand that it’s impossible. So there isn’t much that we can do. We’re so sorry,” finished Konny. “We even discussed your situation with Dr Sabrina Tosi in the UK, and she said the same thing. The only additional suggestion she had was performing a karyotype analysis of the dogs, which I understand you’ve already done.”

“It’s OK. I guess I’d better get going then,” said Steve in a disheartened tone.

“Actually,” started Hartmut slowly, “I wanted to ask you for a huge favour.”

“Sure! Anything!”

“I told my kids about you, and they were wondering if you could come over. They want to fold you into a paper plane. Hey, where are you going?”

“I’ve got to catch my flight! Auf Wiedersehen!!” he shouted as he got into a cab.

CHAPTER 13

Next, Steve flew to Spain to visit Dr Xavier Estivill in the Genome Centre in Spain. Steve had been looking forward to meeting with Dr Estivill and he had high hopes that he would have some good ideas to work on.

Indeed, Dr Estivill did not let Steve down. He went to work right away looking for unique copy number polymorphisms in Steve's DNA that may be associated with flatness. They used the new array CGH chips that Dr Mansour Mohammed had recently made at Quest Diagnostics.

Steve waited anxiously for the results. His nerves were getting the best of him and he started pacing around the lab, making all the staff members edgy as well. Finally, Dr Estivill approached Steve and said,

"Steve, why don't you go for a walk around this beautiful city of ours? You should take advantage of this trip and relax."

"Relax!?! Are you kidding me? I'm in a huge rush to be normal again. I can barely sleep, and you expect me to relax?!"

“Well, Steve, I hate to say this, but you can’t stay here. You’ll have to go somewhere else while we do our work.”

“OK, when should I come back?” he asked.

“You’ll know from our door when we’re done,” replied Dr Estivill.

Steve had long since dominated the art of door-angling to indicate availability, and he entirely understood what Dr Estivill meant.

Steve went for a walk around the city, but couldn’t concentrate. He kept going back to the lab every 1-2 hours to see if Dr Estivill’s door was open, but it was always closed or slightly ajar. It took two days for him to finally find the lab door completely open, and his heart leapt with excitement. He ran inside, but he could tell immediately from the look on Dr Estivill’s face that there were no results.

“I’m sorry Steve. There were several copy number polymorphisms unique to your DNA that might possibly be associated with flatness, but unless we find more flat patients, it’s impossible to draw any conclusions.”

Steve was distraught. But he knew that he had to continue on with his trip, “Well, maybe we can get Dr Mohammed to make a chip for dog.”

“I think that it will take several years to accomplish that,” replied Dr Estivill. “Before you leave, I was wondering if you could help me out,” he continued. “I’ve been meaning to ask you this for a few days. I dropped a sample behind our double door fridge. It’s pretty heavy and we can’t budge it, so I was wondering if you could slip behind the fridge to get it?”

“Sure!” said Steve. “It’s the least I could do after all you’ve done for me.”

Steve peered behind the fridge and saw years worth of dust and garbage accumulated. “Umm… On second thought, I think I’m late for my flight to Sweden. I’d better run!” And fled as quickly as he could.

CHAPTER 14

Steve flew to Sweden to meet with Dr Juha Kere. As soon as he stepped into the lab, Dr Kere greeted him and said, “Steve! It’s good to see you. I tried to call you in Spain, but they had told me that you had already left. I wanted to tell you to cancel your trip to Sweden.”

“What!?”

“I don’t think I can help you. I’d need a whole population of flat people for the analyses I have in mind. But I told Katariina Hannula about your situation, and she wants to test you for segmental UPD. It might be worthwhile since you’re here already. You could also go to visit Ulpu in Finland. She was interested in examining you.”

Steve’s DNA was sent to Dr. Hannula for the analysis. He briefly visited Dr Ulpu Kere, but she looked at the results of Dr Hegele’s examination, and she had nothing to add to it. He spent a few days in Finland and Sweden and where he gave several talks about the research

being carried out in his labs. All the auditoriums where he spoke were packed, and he felt quite honoured by the crowds (although most of them had come to see *him*, not his talk). During one of his talks, Steve was suddenly paged to Dr Kere's office. He abandoned his lecture and ran as quickly as he could to the office. He thought that they must have received important results, otherwise he wouldn't have been urgently paged. When he arrived in his office, Dr Kere rushed towards him saying, "Steve, I'm so happy to see you!"

"Have you got any results?" asked Steve nervously.

"Results? No! Actually, yes! But there's no UPD. Anyway, I locked my keys in my office. I was just wondering if you could get them for me."

Steve sighed, "Sure... Why not?"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CHAPTER 15

Next, he flew to Italy. He was surprised to see Dr Dina Iazano in the airport. After their initial greeting, he asked her how she knew he was coming.

"Well, I read about you in 'Mutant of the Month' on Nature Genetics. I called Jo-Anne to see how you were, and she gave me your itinerary," she explained. "I came to tell you that you should go visit Dr Elena Belloni in Milan."

Steve replied saying, "That's actually where I was headed. Brilliant minds think alike."

Dina drove Steve all the way to Milan, where they met with Dr Belloni. She almost fainted when she saw him, and it took several minutes before she could concentrate enough to hear his story. After listening to

the tale and paying close attention to his family history of flatness, she said "Steve, it seems to me as if all your organs have been predisposed to flatness, meaning that an important mutational event occurred very early in embryogenesis, yet it was not a lethal event. Have you thought of looking at a model organism that might have the same variation?"

"What did you have in mind?"

"The tapeworm. We can look at conserved developmental genes that have unique changes in active sites in the tapeworm."

Steve thought that this was an excellent idea, but when they went to work they realized that the sequence of the tapeworm had very low coverage. They would probably have to spend a year or two sequencing

the entire tapeworm genome before even beginning their evolutionary analysis. Steve was on a much tighter schedule than that.

CHAPTER16

While still in Italy, he received a phone call from a former collaborator, Dr Giovanni Traverso, who had heard about his condition and wanted to meet with him. Steve changed his itinerary and flew out to the University of Cambridge in the UK.

Dr Traverso seemed very excited to meet with Steve and began saying, “Dr Belloni told me about all the difficulties that you’ve been having trying to find enough samples and the lack of RNA. I think I may be able to help you.”

“You can?” asked Steve eagerly.

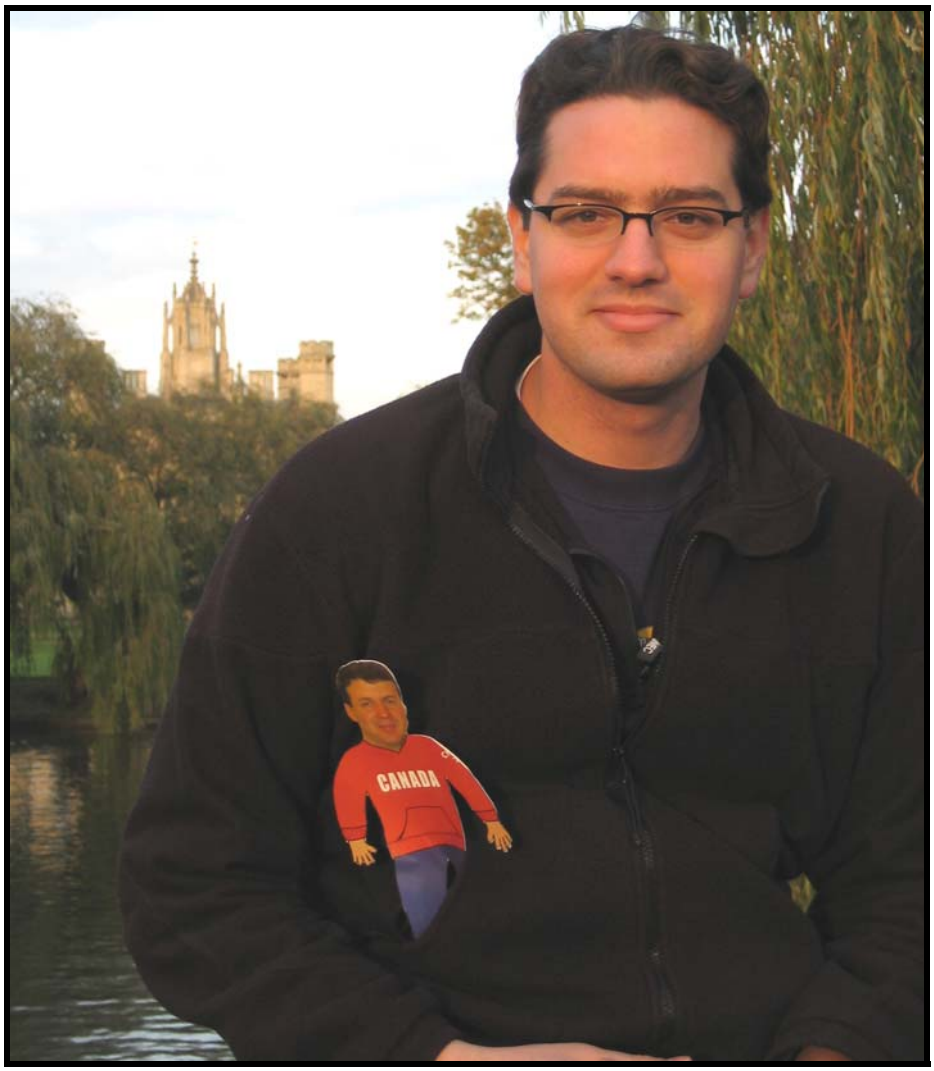
“Well, as you may know, I’ve developed several tests to detect colorectal cancer in patient stool samples. I have a new technique in

mind to extract RNA from stool, and I'd like you to be our 'guinea pig' per se."

"RNA from stool?"

"I think it's an excellent method to extract RNA when blood is unavailable, as has been your case due to flatness. There may be other cases where this method could be used: allergies to the metal used in the syringe, thin veins, delicate skin, lack of clotting… The list just goes on and on… I think that you should be our subject for this analysis."

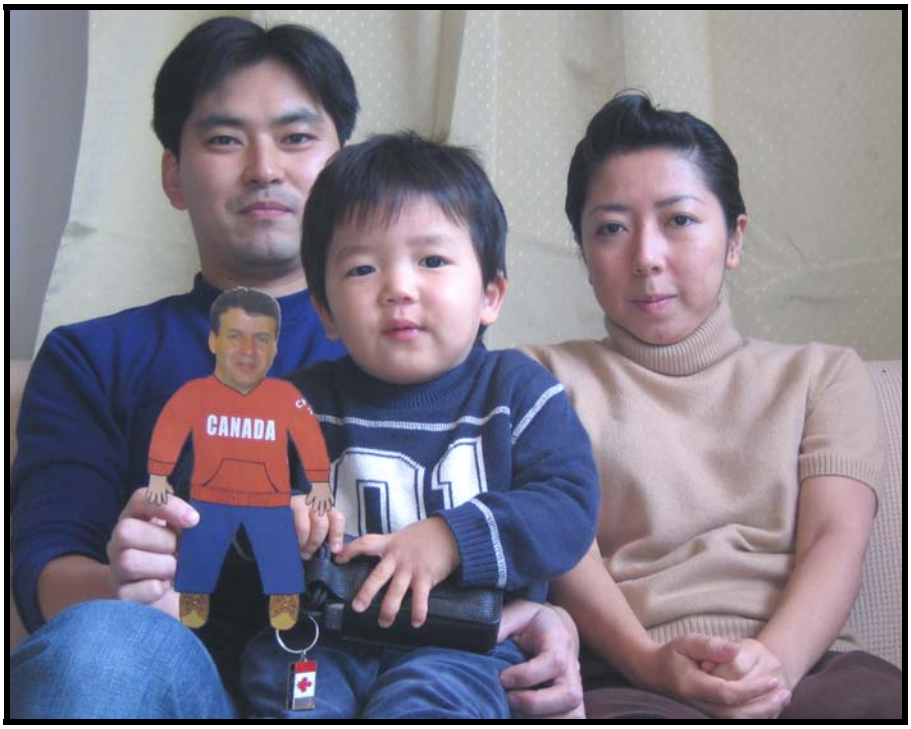
Steve thought about it for quite some time. As desperate as he was to overcome his flatness, the thought of extracting RNA from stool seemed too strange to him, and he couldn't go through with it.



CHAPTER 17

His next flight was to Japan, with a lay over Austria. He took advantage of this and met briefly with Dr Erwin Petek, where they exchanged ideas, but didn't come up with anything.

In Japan, he met with Dr Kazuhiko Nakabayashi. Dr Nakabayashi took Steve to Sapporo to meet with Dr Takahiro Yamada. For the first time since his accident, Steve was glad for his flatness when he boarded the subway in Tokyo on their way to Sapporo. They both hoped that Dr Yamada may have had a flat patient in the past, but their hopes were shattered when they met with him.



Dr Yamada and Dr Nakabayashi discussed Steve's condition for several hours, and they decided that they couldn't determine whether the gene causing flatness was imprinted or not with the materials they had.

They took Steve to other collaborators in Japan, but both Drs Takeyori Saheki and Keiko Kobayashi were stumped. When they exited Dr Saheki's office, Dr Nakabayashi made a surprising remark:

"Steve, you shouldn't be disheartened, because we have a cure for your flatness,"

"You do? What is it? What are you waiting for?" exclaimed Steve impatiently.

"Actually, it's an ancient Japanese cure for many things," explained Dr Yamada.

"Sake!" they both said in unison.

CHAPTER 18

Steve had only one more place to go to on his itinerary: Hong Kong. He was going to meet with his former supervisor, Dr Lap-Chee Tsui, to ask him for any advice. Unfortunately, Dr Tsui was quite busy during the first two days of Steve's visit. He finally had time to talk to Steve, and he suggested that they go to a restaurant to chat.

Steve told Dr Tsui about his trials and tribulations: the accident in the lab, the flat cells, the lack of positive results, the food fight in the academic lab, his problems with the government, and his endless travels, which had been fruitless to date. Dr Tsui listened attentively to Steve's saga, and then thought in silence.

Steve waited for several minutes while Dr Tsui sat deep in thought. "This is taking a lot of time. He'd better have some ground-shattering, mind-numbing suggestions," thought Steve.

The silence was broken by a waiter who came to take their order. Dr Tsui ordered their food, but before finishing, he turned to Steve and said, "I think this food will make you feel better." Needless to say, Steve doubted this very much.

They continued sitting in silence until their food finally arrived. Once it did, Dr Tsui passed a plate to Steve and said, "You should try some of this."

"What is it?" Steve asked.

"It's pufferfish," he replied.

"Isn't that dangerous?"

"Yes, but it's a delicacy here in Hong Kong. The chef here is well known for his skills in preparing pufferfish. I suggest you have some."

"Well… I'm not sure," said Steve doubtfully.

Dr Tsui pressed on, "I insist. You should have some."

Steve pondered for a while longer, and then took the plunge. The pufferfish was a quite savoury and he took his time eating it. After swallowing it, he turned to Dr Tsui, who was staring intently at him and said, "That was really good. Do you think we could order some more?"

The words were barely out of his mouth, when he sensed that something was wrong. His whole body was tingling and his stomach felt bloated. He looked down at his feet, and he realized that they were bursting out of his flat shoes. He was gaining volume! He was still in awe at what was happening to him, when he looked over at his former supervisor who was smiling.

"Fugu, Steve. Blowfish!"

Steve's body continued bulking itself up until it reached its former size. He had no words to express his joy. The only thing he could say was "Dinner's on me!"

CONCLUSION

Steve was finally on his flight back to Toronto. As he rested comfortably in his seat, he pondered on all the events that had taken place and the timeline he had been on. Slowly, he pulled a picture out of his pocket. It was a blurry ultrasound picture of his baby girl: the reason why he had been in such a rush to get home.

THE END


Flat Steve reviews his X-ray findings.
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Flat Steve has his reflexes checked.
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GeneChip® Fluidics Station 450


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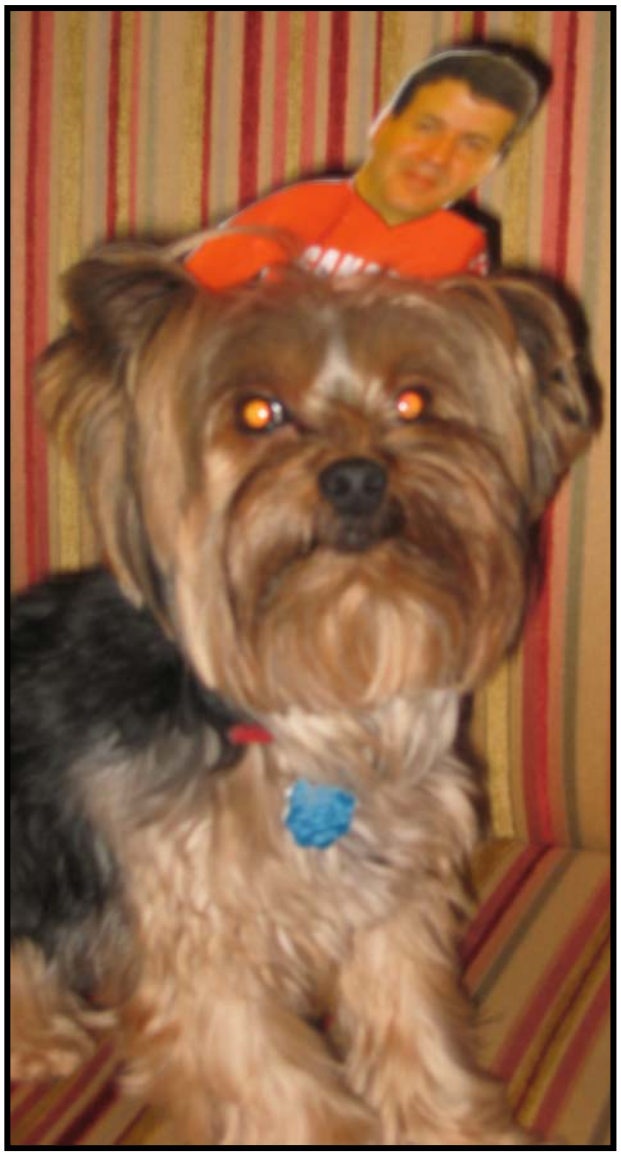

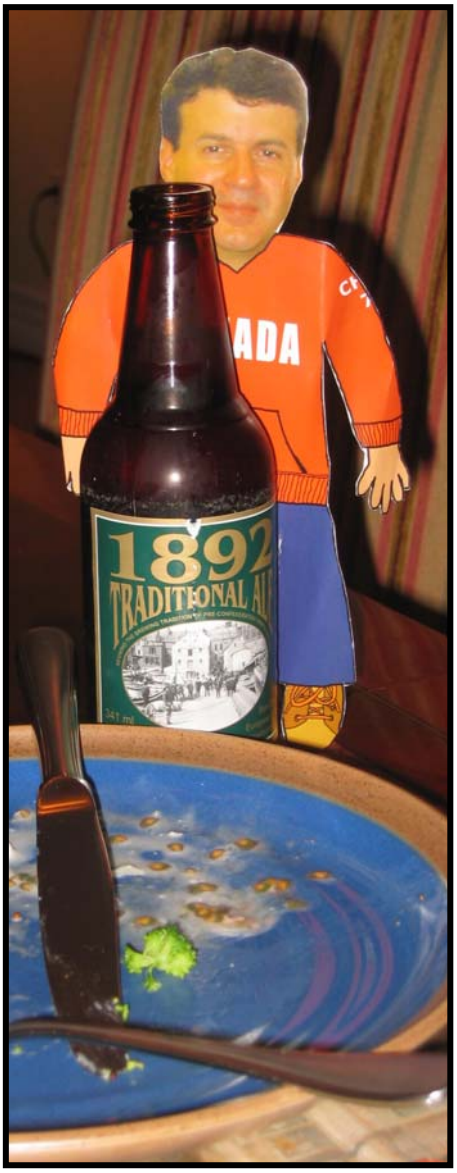
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