In the field of A-T research, few names are bigger than that of Professor Richard Gatti, which will be familiar to almost everyone with an interest in the subject. Professor Gatti was in the headlines earlier this year when his laboratory was awarded nearly $2 million by the California Institute for Regenerative Medicine for its research programmes.

Professor Gatti spoke to me by phone, from his house overlooking the Pacific Ocean in California. Though it was 9.00am there, he had already been working for a couple of hours. His enthusiasm and energy were apparent as he launched into a passionate, detailed and wide-ranging description of his current research.

At the moment, his lab is focusing on a particular type of gene mutation known as ‘nonsense mutation’ (sometimes also called a ‘premature termination codon’ - see box for more information). This kind of mutation blocks the process used by the cell to produce the ATM protein. Their aim is to identify a compound which will help the protein-making mechanism in the cell to ‘read across’ the mutation, effectively ignoring the blockage, and thus finish producing a complete ATM protein.

Similar drugs have already been developed for other conditions which have nonsense mutations. However, a drug for Duchenne's Muscular Dystrophy, called Ataluren, had disappointing results when trialled in patients and was withdrawn. Gatti is very positive about the progress his team are making with the new drug.

While this is an exciting project and one that Gatti clearly believes offers great hope, it must be underlined that it will not help everyone with A-T. This approach can only help those people who have a nonsense mutation. Nonsense mutations only make up about 15 percent of mutations, though they are more common in certain areas of north Africa and central America. However, each person with A-T has two mutations and in areas of mixed population, such as Europe and North America, these are likely to be two different mutations, so the number of people who have at least one nonsense mutation and could thus potentially be helped could be up to about 30 percent.

In order to identify suitable candidates, Gatti’s laboratory has been working its way through a library of 75,000 compounds. They have now narrowed down their interest to a handful of compounds. They have been testing these on a number of key genes, including those responsible for A-T and Muscular Dystrophy, and results have been very encouraging.

One of the challenges particular to A-T is that you need to get your compound into the brain – to the cerebellum to be precise – and the brain is protected by a very effective structure, called the blood-brain barrier. This, as its name implies, is a kind of membrane designed to keep chemicals and cells from the blood away from the brain and the central nervous system.

So at the moment, Professor Gatti and his lab are working to develop ways to get these compounds through the very small ‘doors’ that exist in the barrier.

Once they can do this they will be able to move towards starting clinical trials, and Professor Gatti is hopeful that this is not far off. “I will be very disappointed if by the end of 2012 we are not moving into making an IND application,” he says. An IND (Investigational New Drug) application is the first stage on the route to clinical evaluation and hopefully eventual licensing of a drug.

But as he recognises they “will be entering a whole new world of commercialisation, where there are many obstacles and many sharks swimming around”, to get a drug through the whole obstacle course of testing, approval and ultimately production and marketing will need the support and resources of a pharmaceutical company. And there is the challenge of getting a company interested in a drug that will help a very rare condition.

Professor Gatti is undaunted. “The fact that these compounds can potentially treat a number of genetic conditions is in our
favour. And of course we own the rights to them – that’s essential for the pharma companies to be interested.” And he has a number of potential strategies in mind: “We might be able to ‘piggy-back’ on the interest for treating other conditions, for example Muscular Dystrophy; alternatively we may be able to stipulate in a contract that while they go initially for licensing for another condition, they do A-T second; or we may be able to go for off-label use for A-T.”

And he’s looking for help from wherever he can get it. He has engaged students from the prestigious Anderson Business School at UCLA where he is based to work on the project, looking at how to develop a strong business case and mitigate the risks for potential investors.

The above is a brief summary of a two-hour conversation, which moved ceaselessly from one project or idea to another, leaving this amateur journalist struggling to keep up. Professor Gatti certainly has a huge range of interests, far too many to fit into this article.

I ask him what he is most proud of in his career; he laughs: “Surviving, I guess! No, really, I think the real achievement is having been able to move from a position where we didn’t really understand immunodeficiency at all to identifying and localising the genes responsible for this and to working out how mutations can be repaired. That’s thirty years of hard work.”

He first became interested in A-T when he was a young man, studying with the world-renowned immunologist Professor Robert Good in Minnesota. It was becoming clear that cancer was much more prevalent in children with immunodeficiency conditions and the young Gatti became interested in the links between them. When he eventually began to do his own research, he chose to study A-T, because it caused both immunodeficiency and cancer. He became more and more fascinated by the condition and its underlying mechanisms and has been working on it ever since.

I asked him if he had research interests beyond A-T? He thought for a bit: “Not really though there are other things I find fascinating in A-T, like the whole issue of sensitivity to radiation.

How does he see the situation of A-T research more generally. “I’m very positive” he says. “We are more in touch than ever as a global unit”. And he considers meetings like the one in Frankfurt or that to be hosted by the A-T Society next year as vital, not just for the formal proceedings but for the chance they give experts to talk and spark off new ideas over a coffee or beer.

He also thinks that new technologies are opening up new opportunities. “For example, the great improvements in MRI (Magnetic Resonance Imaging) are potentially very significant for A-T. I’m going to a meeting next week to look at proposals for research using Diffusion Tensor Imaging to look at the nerve tracts that lead from one part of the brain to the next. As well as leading to advances in our understanding of A-T, this could prove very helpful in measuring the impact of new treatments.” He’s also interested in work being done on drugs which affect splicing, another type of problem caused by A-T mutations.

However, the fundamental challenges of A-T research remain. And what are these? “The rarity of A-T, the complexity of its effects and what remains a fundamental lack of knowledge of some of the basic processes, such as how and why the cerebellum is affected and leads to the neurological symptoms.”

And as he approaches the age when most people would be thinking of retiring, I ask about the future; who’s going to take over the torch? “We have that covered” he replies confidently. “There are a number of really good people in my lab who will be taking forward the work.” There are experts on stem-cells and on the clinical side, as well as someone with a special interest in radio-sensitivity. But far from putting his feet up, he’s looking forward to retirement as an opportunity get on with more research. It means he can bow out of all the other tasks and just focus on the research that he loves.

But driven as he clearly is, he does find a little time for relaxation. Richard Gatti is a fine pianist – he studied at the world-famous Juilliard School of Music in New York.
In January this year, Sean Roebig, co-founder with his wife Krissy of the Australian A-T charity BrAshA-T, lost his battle with malignant melanoma.

BrAshA-T has achieved a huge amount to improve the lives of people living with A-T in Australia and to support research, and Sean’s death is a real loss, not just to his family but to the whole A-T community. Sean’s contribution to BrAshA-T will be his legacy and will live on.

The many people who know Krissy either in person or through Facebook, will have witnessed her incredible inner strength and fortitude during the difficult last weeks of Sean’s life. It seems appropriate to let the last words be hers:

"Life is going to be very hard without Sean in it. Raising kids alone is going to be hard. Running the foundation is going to be hard. Going back to work in my shop is going to be hard. Having two sick kids with a disability is going to be hard.

"Getting them to start school for the year is going to be hard. Smiling again is going to be hard... BUT as hard as all of these things will be, it will happen because Sean had faith in me from the day he met me. He loved me. We will be ok..."

### Meet Keck, the assistance dog

By Maureen Poupard

I was delighted to meet the Laage family when I attended the A-T Clinical Research Workshop in Frankfurt last January. Beate and Andreas have one son Christian who is 11 and has A-T. Keck is Christian’s assistance dog.

Keck is two and a half years old and he gives a lot of practical help to Christian. First thing in the morning, Keck finds Christian’s shoes and clothes and brings them to him. He ferries items from mum and dad to put into Christian’s school bag and then accompanies him to school.

There he acts as an intermediary helping Christian make friends. He has increased Christian’s confidence, concentration and independence. With Keck at his side, Christian was able to give a presentation to his class about the Romans, something that would not have happened before.

Keck was trained by the German organisation Vita Assistance Dogs. He is a lively golden Labrador, enjoys being petted enormously and very much has his own personality!

He is great at making friends and is an excellent companion.

Christian controls and praises Keck and feeds him but it is always Beate or Andreas who tell Keck off (if necessary)! This way Christian and Keck always enjoy a good relationship.

Certainly bringing a dog into the family is a big commitment and not for everybody but should you wish to explore this further please contact:

Dogs for the Disabled
01295 252600
[www.dogsforthedisabled.org](http://www.dogsforthedisabled.org)