CHAARM
Combined Highly Active Anti-Retroviral Microbicides

Newsletter
Issue number 3 - 2013

Prof. Robin Shattock

Prof. Charles Kelly

This newsletter marks the end of the third year of the CHAARM programme. During the first part of the programme, much of the research effort has been towards the development of new compounds, improving existing compounds and developing combinations of compounds as candidate microbicides. Formulation studies of the most promising microbicides have also been performed. In the final two years of the programme, the emphasis is increasingly to test the effectiveness of the microbicides in non-human primate models as well as safety in a human clinical trial. Analyses of the human vaginal microbiome and proteome are underway. These studies make use of a large number of fluid samples from African and European groups with the aim of identifying biomarkers for health and disease that may also provide some measure of susceptibility to infection with HIV.

In this newsletter, Dr. Bruce Frank from Particle Sciences discuss the problems and approaches adopted to produce a clinical grade gel coformulation of two anti-retroviral drugs for testing in a phase I trial. Dr. Georgina Morris and Prof. Charles Lacey from the University of York outline the work involved in conducting such a trial. Dr. Roger Le Grand, from the Commissariat à l'énergie atomique et aux énergies alternatives, describes studies in non-human primates aimed at testing microbicides and developing improved challenge models that may more closely resemble events in HIV infection of humans. Other contributions emphasise the importance of comprehensive testing of efficacy and safety of candidate compounds as well as the wide breadth of expertise in the CHAARM consortium.

We look forward to the annual consortium meeting again to be held in Camogli, Italy. Joining us for the meeting will be some members of a new EU-funded project (MOTIF) aimed at developing generic coformulation procedures for ARV-based microbicides and investigating drug distribution across mucosal tissue. This relatively small consortium includes mostly CHAARM participants but also the University of Aberdeen.

This has been another productive year for CHAARM and we thank our dissemination partners, Minerva and EATG, for their continuing work to publicise the CHAARM project.

Prof. Charles Kelly, King's College, London, UK
Prof. Robin Shattock, Imperial College, London, UK

Coordinators of CHAARM project

The project

SEVENTH FRAMEWORK PROGRAMME

Euproject funded by the European Commission

Combined Highly Active Anti-retroviral Microbicides (CHAARM) is a large-scale collaborative project funded by the European Commission (DG research) within the context of the Seventh Framework Programme for technology research and development.

The main objective for the CHAARM project is to develop highly active specific, targeted combinations of microbicides that can be applied at both rectal and vaginal mucosal surfaces to prevent HIV-1 transmission. For the past three years, this project has been focusing on the discovery and development of inhibitors of HIV-1 for use as microbicides, as well as determining the microbicide potential of combinations of established anti-retroviral agents.

The rationale for investigating combinations is both to increase the barrier to the development of resistance, and to increase efficacy through additive or synergistic effects.

In addition to investigating novel combinations of established compounds, the CHAARM project has successfully been able to design new microbicides which are aimed at already established and new targets in order to maintain the pipeline of promising highly targeted compounds. In parallel, studies of mucosal biomarkers have now been performed to determine parameters associated with health and provide a basis for assessments of changes likely to be associated with mucosal damage.

The project has also provided training to young scientists to engage with stakeholders and to disseminate research findings and achievements not only to scientists, but also to a wider audience.

The CHAARM consortium is expected to contribute significantly to the development of single or combined microbicide products for prevention of HIV-1 infection at rectal or vaginal mucosae.

The CHAARM consortium includes partners not only from universities and research institutes but also industrial partners with experience in producing anti-retroviral drugs and a major microbicide developer. Moreover, the partners from universities/research institutes have extensive experience in product development and in the provision of compounds for investigation of their microbicide potential.

The CHAARM project is an initiative funded by the European Commission, FP7, with a budget of €12 million.
The project was launched on January 2010 and runs until December 2014.
The consortium is composed of 33 partners.

The CHAARM consortium is composed of :

Coordinator:

- King's College London, UK

Partners:

- Centre of Cooperative Research in Biomaterials, Spain
- Commissariat à l'Energie Atomique, France
- Council for Scientific and Industrial Research, South Africa
- European AIDS Treatment Group, Belgium
- Fondazione San Raffaele del Monte Tabor, Italy
- Gilead Sciences Inc., USA
- Imperial College London, UK
- Institute of Tropical Medicine Antwerp, Belgium
- Instituto de Salud Carlos III, Spain
- International Partnerships for Microbicides, USA
- Karolinska Institutet, Sweden
- Katholieke Universiteit Leuven, Belgium
- Microbiotec srl, Italy
- Middlesex University Higher Education Corporation, UK
- Minerva Communication, Belgium
- Mintaka Foundation for Medical Research, Switzerland
- Particle Sciences Inc., USA
- Polymun Scientific Immunbiologische Forschung GmbH, Austria
- Queens University Belfast, Ireland
- Spoluka Chemical Company Ltd., Ukraine
- St George's Hospital Medical School, UK
- Tibotec-Virco Virology, Belgium
- Università degli Studi di Roma "La Sapienza", Italy
- Università delgi Studi di Siena, Italy
- Universitaet Basel, Basel Switzerland
- University College London, UK
- University of Antwerp, Belgium
- University of Geneva, Switzerland
- University of LIverpool, UK
- University of Utrecht, The Netherlands
- University of York, UK

by Minerva Consulting & Communication

"Clearly the field of microbicides development remains a fascinating area of research."

ITM of Antwerp, Dr. Guido Vanham

The Institute of Tropical Medicine (ITM) of Antwerp has been involved in vaginal microbicide research from very early on in the HIV epidemic. Because of early failures with non-specific products, the ITM Virology Unit investigated more specific inhibitors, paying a lot of attention upfront to possible toxicity. Within the context of CHAARM, ITM has developed a number of in vitro material quality tests to evaluate activity and toxicity of microbicides in a standardized way.

What have been the overall results of your tests while at CHAARM?

Over the last 10 years, the Virology Lab has evaluated novel candidate microbicides, including entry inhibitors (e.g. CD4 miniproteins and nanobodies). Amongst the former two classes of compounds, quite a few very potent molecules with nanomolar[2] activity were identified, whereas the activity of integrase inhibitors is still not optimal at this moment. While working with CHAARM, we selected and tested compounds that had a very low cellular toxicity and most combinations showed, nicely, additive effects in activity. In general, results of simple in vitro models were very consistent and they helped us predict the results of other more complex systems, such as cervical tissue. There are a lot of potentially interesting molecules, filling up the pipeline for future animal and clinical trials.

What has been the most important breakthrough that the virology lab has had this year within CHAARM?

Of the tested compounds, the mini-CD4[3], developed by Loic Martin (from CEA) and co-workers has been formally tested in macaques at Roger Le Grand's (also from CEA) facility in Paris and it showed a clear protective effect against vaginal HIV infection. Normally with this class of compounds, not all are equally active against all HIV subtypes, therefore they will have to be part of a combined microbicide with other types of compounds such as reverse transcriptase inhibitors (RTI)[4]. Together with the Medical Chemistry Department at the Antwerp University, we have developed an improved non-nucleoside[5] (NN) RTI, which remains active against viruses that are resistant to other NNRTI, including Dapivirine[6]. We hope that our compound may be a candidate next-generation NNRTI microbicide.

Sitting: Liselotte Hardy, Vicky Cuylaerts and Vicky Jespers
Standing: Guido Vanham, Jordan Kyongo, Kevin Ariën, Said Abdelatti, Jo Michiels

Now that we are halfway through CHAARM, what do you believe the benefit of this HIV research will be? Will all of the research goals be met?

As already suggested, the portfolios of antivirals of several classes that are available in CHAARM have a great potential, especially in combination with eg Tenofovir[7], the only compound until now that has shown significant protection in a human microbicide trial. However, whereas in vitro testing is relatively easy and straightforward, making a combined vaginal formulation that releases the products in a sustained fashion proves to be a challenging task that might not be completed at the end of the program. Nevertheless, the need for easy-to-use, safe and affordable topical prevention options will remain and hence the development of microbicides should and will continue.

What have been some of the benefits of working with CHAARM? How has your involvement with CHAARM impacted other research?

> Thanks to CHAARM, a common wisdom platform of various aspects of drug development has been established.

Academic expertise is often highly specialized and scattered, but thanks to CHAARM a common wisdom platform of various aspects of drug development has been established. This enables us to accumulate a fair amount of knowledge and know-how, which will be profitable, not only for microbicides development, but for the wider field of HIV prevention and therapy.

If there is one piece of knowledge, or words of advice you could present to a young researcher looking into the field of Microbicide, what would it be?

Clearly, the field of microbicide development remains a fascinating area of research, therefore young researchers will have opportunities to bring in new concepts and approaches. It is also very evident that all "specialists" in different disciplines need to think and act in a "trans disciplinary" way to bring useful microbicides against HIV. As an example, we now have two promising PhD students at the ITM working on microbicide related topics. Liselotte Hardy is looking at vaginal Biomarkers in young adolescents in Belgium and she is setting up a model to study biofilm formation in the vagina. Jordan Kyongo is studying Biomarkers to identify factors playing a role in HIV transmission.

by Minerva Consulting & Communication

"You have to be very aggressive and very dedicated to the solution because this is such an important problem."

Particle Sciences, Dr. Bruce Frank

Dr. Bruce Frank, is the head researcher at Particle Sciences located in Bethlehem, Pennsylvania. Their role in the CHAARM project involves the development of gel formulations. Dr. Frank's personal role within Particle Sciences is as project manager and his responsibilities include the organization of the project and work of Particle Sciences, the management of the timelines and the budget for the project and communication with the rest of the CHAARM team. His broad background in Organic Chemistry and Biochemistry provides a good background for his leadership role in projects such as CHAARM.

What have been some of the challenges faced while working in your phase of the project?

Darunavir[8] which is one of the important API[9]s in this gel had some stability issues where we were seeing some related substances to Darunavir start to appear during the stability studies with the gel. It turns out it is very sensitive to its environment and we had a lot of challenges in trying to stabilize that molecule so that it could remain in its intact presentation in the gel for a long enough time. We were able to increase the stability of that compound so that we think that we could get a year's life out of the gel which will go a long way towards the clinical manufacturing of the product.

Are you satisfied with the results achieved? Do you see any advantages, any concrete benefits or opportunities?

Yes. We think that we've stabilized it to the degree that it will be useful in a clinical trial. Our target was to get at least a year's stability out of that and we think that's been achieved so we've met at least our goal of being able to design and manufacture the gel for the clinical trial when the time comes. There are certainly improvements that could be made and we will continue to look at that but as it stands now, the gel should be appropriate for those trials.

Why do you believe gel was chosen by CHAARM as the medium of choice for testing and production ?

There are other formulas possible but we think the gel has the advantage of having a long use history so women are comfortable using vaginal gels. There are other options including capsules, or thin films, dissolving films, that are also very easy to handle and would be I think acceptable, but they have not been used nearly to the degree that gels are so there might be some acceptance issues that may need to be addressed.

Front row: Laurie Goldman, Jacki Kutzler, Kelly Chubb
Back row: Bruce Frank, Garry Gwozdz

What have been some of the benefits of working with CHAARM? How has your involvement with this consortium impacted your research?

I think working with a consortium like this is very important for Particle Sciences. We've worked in the field of Microbicides for seven or eight years and it has always been an important part of our corporate goals, to participate in projects such as this. Being part of this particular collaboration has been important to Particle Sciences because we have been able to interact with leaders in the field of Microbicides research. We've learned a lot and we think we have contributed a lot to the development of the field and I think we will find ourselves in similar projects in the future and certainly hope to make equally important contributions to these. We are very happy to be a part of this.

If there is one piece of knowledge, or words of advice you could present to a young researcher looking into the field of Microbicide, what would it be?

I think you need to come to this field very dedicated and with a lot of energy. It takes a lot of work. You have to be patient because the time frame for getting this done can be long but you have to be very aggressive and very dedicated to the solution because this is such an important problem. You have to come in with the idea that you are going to be the one to find the solution because it is out there and we need to find it. So come with all of your energy and dedication.

Our target was to get at least a year's stability out of that and that has been achieved so we've met our goal of being able to design and manufacture the gel for the clinical trial when the time comes.

by Minerva Consulting & Communication

"Doing research in human subjects requires a lot of preparatory work and permission...it can take a whole year. "

University of York, Professor Charles Lacey and Dr. Georgina Morris

Dr. Georgina Morris is a doctor and a specialist in HIV and, for the past 4 years, Dr. Morris has been developing HIV microbicides and vaccines. With regards to CHAARM, Dr. Georgina Morris is mainly involved with phase 1 clinical research which involves translating new products from animal trials to human trials. Their research involves looking at product safety and drug levels (also known as pharmacokinetics[1]). Both researchers are looking to ensure that when a patient applies the gel product, the drug is safe and remains potent. Prof. Charles Lacey and Dr. Morris also look to make sure that the patient does not experience any soreness or problems with the actual product.

Your organisation has helped with human trials of the formulations developed in the previous portions of these studies, what were some of the challenges faced of working within this phase of the project?

Dr. Morris: The actual period of testing on volunteers is quite an intensive period, ranging anywhere from 6-12 months. It can also take months of recruiting before we even reach the testing phase. This kind of research requires people giving up a lot of their time to test products so it can be difficult to acquire all of the volunteers needed. A lot of times, people must test at home and then come to the clinic so that can be very time consuming for the volunteer. The study we did last year was of the MAB Gel[10] and it had some challenging parts as we tested levels of the antibodies within the volunteers which had to be checked on the 1st, 8th, and 24th hours etc. after dosing. This particular testing can also be very invasive requiring samples from the vagina and blood tests.

Prof. Lacey: Doing research in human subjects requires a lot of preparatory work and permission. It can take a whole year to get to the actual administration of the trial products because we have so many steps to go through beforehand to ensure that Good Clinical Practice is being performed. We have extremely high standards of safety and ethics so it is a long process to reach the actual testing phase. Another thing that can be a bit challenging is the analysis of the data. Taking the results we obtained and seeing what it all means.

Dr. Georgina Morris (left) & Professor Charles Lacey (right) University of York, UK

What have been the overall results of these tests?

Prof. Lacey: Recently, we have been involved in the testing of the MAB Gel we mentioned with Europrise, a forerunner of CHAARM. The results we received were in fact, quite surprising. Of the monoclonal anti HIV antibodies we tested with the volunteers, two of the antibody, 4E10[11] and 2F5[12] achieved vaginal levels as expected yet the 2G12[13] antibody didn't. Subsequently, we did further studies in collaboration with 2 other researchers within CHAARM and we discovered that when we added the vaginal secretions of humans to the 2G12 antibodies in the laboratory, the antibodies broke up. After we identified this issue we were able to address it and make the necessary adjustments.

As the final years of this project come upon us, what do you believe that this HIV research will result in?

Dr. Morris: What we do is in the later stages of the CHAARM project so year 4 is going to be the most important because that is when we will be testing the new combination anti-retroviral microbicides in women. Until now, what we have been doing has been mainly the planning of the pharmacokinetics trials so next year is when we will get into the actual testing.

Dr. Georgina Morris in the lab

Prof. Lacey: Right now we are currently working on the preparatory writing of documents and organizing people who will help with testing. For us, next year will be the most important because we are hoping to finally have the evidence to prove that the combination of two drugs will be more effective than one in the prevention of HIV transmission.

What have been some of the benefits of working with CHAARM? How has your involvement impacted your research?

Dr. Morris: The main benefit is collaboration. When you are working within such a large consortium such as CHAARM, there are a lot of opportunities to collaborate and bounce ideas back and forth.

Prof. Lacey: I agree, working with CHAARM has given us access to quite a range of people from a wide range of countries. With large collaborative projects such as these, we are able to tap into other's knowledge and expertise.

What advice would you give to a young researcher looking into the field of Microbicides?

Dr. Morris: Be prepared to work hard and persevere. It is hard work, like Charles said earlier, it can take several years of planning before you even get to the testing stage. Plus, not all products get to that stage, so it can be hugely frustrating.

Prof. Lacey: Also it is important for people to have some experience in caring for people with HIV and with rectal and vaginal areas if they are looking to get into this kind of microbicide research. It can be quite technical.

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"What makes me confident is that most of the partners have a lot of experience now in the growth and testing of microbicides."

Commissariat à l'Énergie Atomique (CEA), Dr. Roger Le Grand

Dr. Roger Le Grand, has a background in veterinary medicine and obtained a PHD in virology and immunology before working on AIDS vaccines and models for assessing the efficacy of these different AIDS vaccines. Dr. Roger Le Grand began this 20 years ago with a group led at that time by Professor Dominique Del Monde. Dr. Le Grand was partner in EMPRO and then continued with CHAARM and MOTIF, in the same area of prevention of HIV virus transmission. Dr. Le Grand's contribution to this entire program is mainly the development of animal models, and pre-clinical work. The models being used for this portion of the project are Non-Human Primates, and in particular, Macaques that can be challenged with different kinds of viruses.

What has been the highlight or the most important breakthrough that your group has experienced this year through the support of CHAARM?

So far, our major breakthrough is to really identify and characterize cells in the semen of the animals that are infected with the HIV and can possibly transmit the infection during the sexual contacts.

> We all need contributions from all countries. Endeavours for microbicides and vaccines are really very difficult and need a very huge collaboration between people who are experts all around the world.

I think this is one of the few studies that demonstrate that semen can be infectious not only through the free virus particles present in the semen but also through the infected cells that are in the semen. If we can confirm that both free and cell-associated virus can transmit infection, it will be very important that we develop vaccines or microbicides that can affect these two kinds of infectious materials.

This year, we were working on mechanism understanding of the transmission, and we have also started. Year pharmacokinetic studies (or PK studies) of a combinations of antiviral

Dr. Roger Le Grand, Commissariat à l'Énergie Atomique, France

drugs used as microbicides; we don't have the results yet, and that will be coming soon, so next year we will be able to discuss the results obtained in the animals and that will help in the design of the future trials, either in the animals or the clinical phases. So the major issues we have to face in preparing these PK studies are more on the formulation part and once we put the compoud into vagina of the animals, how to collect the samples in order to preserve the drugs.

If there is one piece of knowledge, or words of advice you could present to a young researcher looking into the field of Microbicide research, what would it be?

Yes, 1st they should not fear these kinds of studies. I think it is important that young people really approach the field from the beginning by thinking of strategies that will have an impact on transmission. The 2nd piece of advice is to not think it will be simple. There are two very important things, the actions of the drugs and kinds of transmission of the viruses. These two things are still to be explored in depth in order to be innovative in producing new compounds and strategies that may really affect transmission of the virus and have an impact on the epidemics.

Do you think Europe is at the cutting edge of Microbicide research or do you think it needs contributions?

We all need contributions from all countries. Endeavours for microbicides and vaccines are really very difficult and need a very huge collaborative effort between people who are experts all around the world. I think Europe is well positioned though. One of the major advantages to working in Europe is that we have a very strong network of people that know each other very well and know how to collaborate on projects such as CHAARM. I believe this networking is one of the best strengths we have for the future.

As the final years of this project come upon us, what do you believe that this HIV research will result in?

I'm very positive and I would not say that if I had not participated with the previous program, EMPRO. I think that being in the middle of the program is the most difficult situation for assessing in terms of achievement where we are going with our goals. Certainly, the most important results will come next year or the year after, when we have our first real efficacy trails and clinical trials with humans. At the end of all this, we will have a nice picture of where we are going. What makes me confident is that most of the partners have a lot of experience now in the development of microbicides and testing microbicides. They all have more than ten years experience in the field and we know that the combinations we have selected for these programs are very promising in terms of microbicies.

by Minerva Consulting & Communication

"We have moved to a new facility just outside of Vienna and have had an increase in manufacturing capacity."

Polymun Scientific, Dr. Dietmar Katinger

Dr. Dietmar Katinger has been the CEO of Polymun Scientific since December 2010. Within CHAARM, Polymun supplies 3 neutralizing antibodies for pre-clinical studies. Dr. Katinger has worked with researchers currently involved with CHAARM previously as a partner in an earlies. The reagents partially kept in store are manufactured by Polymun as required.

Were there any challenges faced in distributing reagents to consortium members? How were these challenges addressed and overcome?

There are not many challenges. We do this every week because we sell reagents for research so it is a routine process. Some reagents are very easy to manufacture and others are more difficult. It just depends. Aside from the CHAARM project, we ship neutralizing bodies worldwide but it is not much of an issue. This is especially so, because the shipments we send to CHAARM are fairly local shipments, we rarely send things too far away for the CHAARM project.

Which specific antibodies and antigens were distributed to consortium members? Was there a pre-determined formulation Polymun replicated and distributed?

In this case, we sent CHAARM neutralizing agents. They are the most relevant. The specific bodies distributed to CHAARM were already in stock and were requested by them. They include 4E10 2F5 and 2G12. These antibodies were already established by us, the new idea involved around CHAARM was to use them as a microbicide.

Dr. Dietmar Katinger, Polymun Sciences, Austria

Is there a specific process that is entailed with the packaging and preparation of this distribution? What variables had to be taken into consideration? Please explain.

The distribution process is rather simple, there is a contact person who provides an address and the reagents are sent via FedEx. The reagents themselves are packages in small plastic vials and are placed in cool packs to maintain a cool temperature. There are usually 10 milliliter tubes and 50-100 microliter tubes. They must be kept at 2-8°C. This temperature is the only variable that we have to be careful with but it is easily controlled with the ice packs.

New Location, Polymun Sciences, Austria

What have been some of the benefits of working with CHAARM? Has your involvement impacted Polymun's own research?

Aside from the small role Polymun has had in this particular project compared to the others, there is generally a very good network that has resulted from many of these research projects. We most definitely hope to remain in contact with this network. The most positive aspect is the overall exchange of information among researchers that goes on. Also, working on current projects leads to new contacts which may later use Polymun for the provision of reagents in future clinical studies. This has already happened where contacts have talked with groups who have used our services and they later use Polymun for their own clinical studies.

In this particular project compared to the others, there is generally a very good network that has resulted from many of these research projects. The most positive aspect is the overall exchange of information among researchers that goes on.

Is there anything else you can tell us about your work with the CHAARM project or your own personal work?

There have been developments in terms of the new research going on in Polymun but the most significant thing is the recent expansion of Polymun. We have moved to a new facility just outside of Vienna and have had an increase in manufacturing capacity. In these new facilities we have three times as much space as we did at our older facility.

by Minerva Consulting & Communication

Challenges faced and overcome: Progression & Collaboration marks the year 2012 for CHAARM Consortium.

As the third year of CHAARM draws to a close, we look back over this past year at the performance of the project and the progress made by researchers within the CHAARM consortium.

One of the main goals in 2012, was to produce a clinical grade gel formulation containing two anti-retroviral drugs for testing as a microbicide.

Work carried out this year has revealed both exciting breakthroughs as well as tough challenges that will need to be overcome in order to get closer to meeting the main project objectives of developing combinations of highly active specifically-targeted microbicides to stop the spread of HIV. Due to the collaborative nature of the project, significant progress has been made within the required time-frame, and this article will highlight the important findings that have been reported this year.

Major findings during 2012

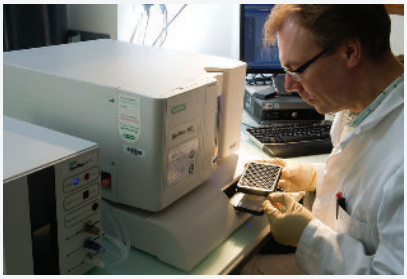
Formulation

One of the main goals in 2012, was to produce a clinical grade gel formulation containing two anti-retroviral drugs for testing as a microbicide. Dr. Mark Mitchnick and Dr. Bruce Frank from Particle Sciences have developed a gel coformulation of the antiretroviral drugs Darunavir and Dapivirine that can be tested in macaque pharmacokinetics/pharmacodynamics (PK/PD) studies and in a human safety study. Dr. Karl Malcolm's group at Queen's University, Belfast, have developed sustained delivery formulations (intravaginal rings) dapivirine and darunavir both separately and in combination.

Researcher from the University of York, UK

Drug discovery

Studies into drug discovery have also generated exciting findings. Work in Prof. Koen Augustyns's group at the University of Antwerp, has identified a novel compound that potently inhibits an essential viral enzyme (reverse transcriptase). This compound is currently undergoing further development and testing. Dr Loïc Martin and colleagues at the Commissariat à l'Énergie Atomique have developed a small molecule that mimics the host receptor (a cell surface protein known as CD4) and acts as a decoy to prevent HIV from entering and infecting cells. A gel containing this molecule was tested in rhesus macaques and gave complete protection against viral infection. The findings were published this year in the on-line journal Plos Pathogens. Prof. Theo Verrips, University of Utrecht, and Prof. Robin Weiss, University College London, have isolated a single domain llama-derived antibody with potent and broad spectrum neutralising activity against HIV which was effective against 96 out of 100 HIV-strains tested in the laboratory. This antibody will be formulated into a gel with the aim of progressing to efficacy studies in macaques. Finally, Prof. Oliver Hartley's group at University of Geneva/Mintaka have generated a highly active compound that prevents HIV from binding to an essential coreceptor on the cell surface and so blocks infection. With additional support from other funding bodies, this group has established manufacturing and formulation procedures that can be used to produce a microbicide that is suitable for testing in humans.



Researcher from the University of York, UK

Testing

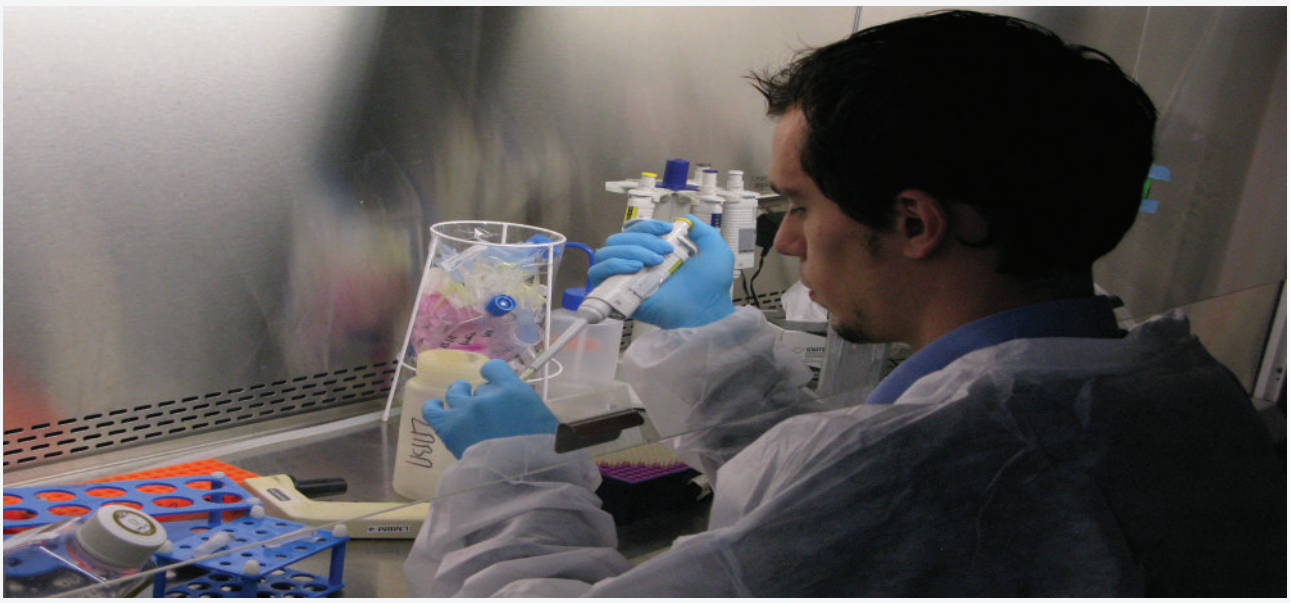
Researcher from the University of York, UK

To date, Dr. Guido Vanham's group at ITM has tested over 250 compounds with anti-HIV activity to determine which are the strongest candidates for further development as microbicides. These include those discussed above. Equally importantly, colleagues at Imperial College, Institute of Tropical Medicine Antwerp, Katholieke Universiteit Leuven, Fondazione San Raffaele del Monte Tabor, Instituto de Salud Carlos and Tibotec-Virco-Virology have established an integrated platform that uses a battery of tests to select the safest and most effective potential microbicides that can be developed further within CHAARM.

To date, Dr. Guido Vanham's group at ITM has tested over 250 compounds with anti-HIV activity to determine which are the strongest candidates for further development as microbicides.

Dissemination of Results

In 2012, CHAARM consortium members attended International Conferences to give oral and poster presentations of their work. Microbicides 2012, was held in Sydney, Australia in April and 9th Con-

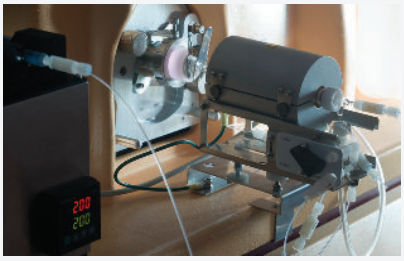


ference on Retroviruses and Opportunistic Infections (CROI) was held in Seattle, USA in March, with many of consortium members attending. In addition, during 2012 many groups have published their findings in peer reviewed journals.

With large collaborative projects such as CHAARM, we are able to tap into other's knowledge and expertise.

Collaboration between partners

The collaborative nature of this project has ensured that during 2012, most of the deliverables have been met and milestones have been achieved. Many researchers believe that there are many benefits and opportunities to be gained from working in a collaborative project. Prof. Charles Lacey from the University of York says "Working with CHAARM has given us access to quite a range of people from a wide range of countries. With large collaborative projects such as these, we are able to tap into other's knowledge and expertise". Dr. Roger Le Grand from the Commissariat à l'Énergie Atomique (CEA) comments on the collaborative nature of CHAARM saying "It is certainly the result of European policy in research that forces us from the beginning to build these networks that I believe have now become very efficient".



Looking to the future

Since its inception in 2010, CHAARM has been steadily making progress, both in the achievement of its objectives and overcoming the challenges that have been presented.

"It is certainly the result of European policy in research that forces us from the beginning to build these networks that I believe have now become very efficient".

During these last two years of the project, there will be greater emphasis on in vivo studies and human studies. Challenge studies will be carried out in macaques as well as the Phase I clinical trial of Dapivirine and Darunavir, which will be carried out by Prof. Charles Lacey at the University of York. Furthermore, characterization studies of cervico-vaginal biomarkers will be carried out by St George's University of London, University of Liverpool and the Institute of Tropical Medicine, Antwerp.

Regardless of whether a major breakthrough in the field of microbicides will be found before the completion of the project, CHAARM researchers remain optimistic about the future of microbicide research. "I believe there are going to be solutions out there" suggests Dr. Bruce Frank, "I believe there are a lot of smart people who have not gotten into the field yet that could be the ones to come up with this breakthrough, so I believe this research should continue for no other reason that it is life and death".

In the development of effective microbicides, it is important to understand that the road to success is a long one with many setbacks on the way. As Prof. Charles Lacey points out "People have to realise that it does take time to get a quality product out there. People just want you to go ahead and give them something great, but it takes a lot of time and research, so it is important that the public really understand that".

However, due to successful collaborations within the consortium leading to the achievement of project objectives, the future of CHAARM remains bright.

Researcher from the University of York, UK analyzing results of experiments

Future Events 2013 / Glossary

11th European Meeting on HIV & Hepatitis March 20-22; Italy, Rome
Following the 10th edition of the meeting in Barcelona, the 11th European Meeting on HIV & Hepatitis - Treatment Strategies & Antiviral Drug Resistance, to be held on 20 - 22 March 2013 in Rome, Italy.

14th International Workshop on Clinical Pharmacology of HIV Therapy 2013, April 22-24; Liverpool, United Kingdom

Following the success of the 18th Annual Conference of BHIVA, held in 2012, the 19th Annual Conference to be held in the spring of 2013 at Manchester Central Convention Complex, located in the heart of the city.

19th Annual BHIVA 2013, April 16-19; Manchester, United Kingdom
14th International Workshop on Clinical Pharmacology of HIV Therapy will be held on April 22 - 24, 2013. This is prior to the EASL International Liver Congress, which will be held in Amsterdam, The Netherlands on April 24 - 28, 2013.

International Conference for Academic Disciplines (Provence 2013), May 14-17; Aix-en-Provence, France
Various academic disciplines converge on Provence's medieval villages amidst plush fields of lavender, vineyards and olive groves. Research presentations and bus tours make up an unforgettable 4-day conference.

9th International Workshop on HIV & Hepatitis Co-infection, May 30-31; Italy, Rome
This annual workshop is the leading medical gathering for those involved in the clinical care of co-infected individuals. The program provides an excellent platform to exchange the medical information and new treatment results, and to discuss them with the experts' active in the different disciplines (including Virology, Hepatology, Immunology, Infectious Disease and Primary Care).

STI & AIDS World Congress 2013, July 14-17; Vienna, Austria
During the conference, you will experience a scientific program of very high quality, reflecting the broad range of STI/HIV science and clinical practice. We are expecting the largest attendance of all ISSTDR/IUSTI joint conferences and a large number of abstracts on the current research work.

EACS 2013 October 16-19; Brussels Belgium
As a special feature the 15th International Workshop on Co-morbidities & Adverse Drug Reactions in HIV will be affiliated with this EACS conference to allow for stimulating synergies in addressing issues concerning long-term care which are of common interest

2nd Antivirals Conference November 11-13; Cambridge MA, USA
The Congress will be supported by Antiviral Research, the most comprehensive and pre-eminent journal for those interested in the effective control of virus infections in animals and man as well as in plants or lower organisms.

BHIVA World AIDS Day Event November 28; London, United Kingdom

GLOSSARY
TECHNICAL TERMS

[1]**Pharmacokinetic studies-** research which involves looking at product safety and drug levels

[2]**Nanomolar-** unit of measurement of any molecular species in a substance

[3]**mini-CD4-** promising class of protein that prevents HIV from entering a healthy cell

[4]**Reverse Transcriptase Inhibitor (RTI)-** drug that inhibits the process known as reverse transcription which is needed for the replication of retroviruses such as HIV

[5]**Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-** an antiviral drug used against HIV that prevents RNA conversion to DNA and is often used in combination with other drugs

[6]**Dapivirine-** microbicide that inhibits virus replication in healthy cells

[7]**Tenofovir-** class of antiretroviral drug which blocks enzymes (called a protease or peptidase) crucial to viral production

[8]**Darunavir-** an antiretroviral enzyme inhibitor used to treat HIV

[9]**API-** active pharmaceutical ingredient

[10]**MAB Gel-** monoclonal antibody gel formulation used in Phase I of the Human Trails

[11]**4E10-** a neutralizing antibody which targets the membrane of the HIV-1 envelope protein

[12]**2F5-** a neutralizing antibody which targets the membrane of the HIV-1 envelope protein

[13]**2G12-** a neutralizing antibody which targets the membrane of the HIV-1 envelope protein

CHAARM
Combined Highly Active Anti-retroviral Microbicide

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