



The African Chip: Challenges, Successes and Possibilities

by Rehab Ahmed and Nicola Mulder

African scientists, together with international collaborators and funding agencies, are leading an initiative, the *African Chip Project*, which is expected to make a difference in the fields of Genomics and Genomic Medicine in Africa. This work was recently described by Bill Gates as “exciting progress” through a public twitter message.



To shed some light on this impressive project and progress to date, we interviewed Professor Nicola Mulder of the University of Cape Town (UCT), a prominent African scientist and leader of the African Chip Project.

First, let's talk a bit about yourself?

I run the Computational Biology Division at UCT where I supervise and teach a number of postgraduate bioinformatics students and provide bioinformatics support to local researchers.

However, most of my time is taken up by my role as PI of H3ABioNet, the Pan-African bioinformatics network for H3Africa. My research interests are in the use of bioinformatics to address human diseases in Africa.

This is very diverse, as reflected by the diverse projects in my group, from studying bacterial pathogens and host-pathogen interactions, to microbiomes, to human population genetics and disease. The makeup of my lab is equally diverse, with students from about 10 different African countries!

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What are chips? Why are they important? And why do we need a chip that is designed for African populations?

A chip is an array format where multiple measurements can be made on the same sample simultaneously. A genotyping chip contains probes that differentiate reference from alternative alleles, enabling one to determine genotypes in samples at multiple different positions. They provide an accurate and cost-effective way of identifying multiple SNPs, or markers, (usually millions) at the same time. Doing this by sequencing is still expensive. The current arrays on the market were developed using existing population genetic data which is heavily biased towards Europeans. Therefore, their efficiency in African populations is suboptimal.

What is the basis for this African chip? Or in other words, what was the approach to the customization of this chip?

The chip was designed using about 3500 sequences from African populations, including the 1000 Genomes African populations, data from the African Genome Variation Project, and sequencing done on H3Africa samples through the research projects or supplementary funding from the NIH. The base of the chip is 1.8 million markers from existing chips with the same technology, and we were able to add ~800,000 custom SNPs. For this, we got request lists from H3Africa researchers, selected SNPs of functional interest (GWAS catalog, PharmGKB, ClinVar, etc.) and then used the sequence data and minor allele frequency information to select the remaining

SNPs to represent the haploblocks across the genome. There were several rounds of selection and evaluation.

Who is involved in this project and who led this initiative? What company are you working with?

The main project is being led by Dr Zane Lombard and Dr Adebowale Adeyemo, as chairs of the Genome Analysis Working Group. There are several different aspects to the initiative in which different people were involved, including finding sequence data and new samples for sequencing, negotiating with the companies, and the actual technical design. For the technical design, I have taken the lead, but working closely with other teams. A group at the Wellcome Trust Sanger Institute led by Dr Manj Sandhu did the processing and variant calling for all the low coverage data, my team at UCT did this for the high coverage data. Some of the high coverage data alignment and variant calling was done in collaboration with Prof Victor Jongeneel's team at the University of Illinois, as the high coverage data were processed at their Blue Waters facility. Members of his team put a lot of work into this part of the pipeline.

For the rest of the design, we have had a smaller team from UCT and Wits. The team at UCT includes; Gerrit Botha, Dr Emile Chimusa Ayton Meintjes, and Mamana Mbiyavanga, and the Wits team includes; Dr Ananyo Choudhury and Prof Scott Hazelhurst who have been instrumental in finalizing the custom SNP list. There are several others who played a role in



the selection of some custom SNPs through their expertise in specific areas. In addition, the Bioinformatics Service Platform staff at the Centre for High-Performance Computing (CHPC) in Cape Town helped facilitate access to their compute resources, and members of eResearch and ICTS at UCT helped with resolving data transfer issues and facilitated access to UCT's HPC. Illumina is the company who will manufacture the chip.

When was the work on the chip started? And when will it be ready for researchers? Will it be affordable for researchers and clinicians (especially those based at African institutions)?

Work started about 2 years ago; it has been a long and arduous process. Manufacture is starting now, which should take several weeks. The chip will be available for \$55 for H3Africa consortium members. Illumina has offered to run samples on the chips at their central facility for \$15 per sample (over and above the cost of the chip).

Are you thinking of providing a genotyping service using this chip? Some institutions might not have the necessary infrastructures to use it, and it would be encouraging if a specific center is helping here in terms of wet lab or the data analysis.

Not me personally! The CPGR in Cape Town won the bid to have a free iScan equipment placed at their company to provide a genotyping service. This will only happen later this year. As mentioned above, researchers can use the central Illumina facility.

What are/were the challenges for this chip?

MANY!! The data we were dealing with are large and took a lot of computing and storage. The actual processing of many stages of the pipeline were computationally intensive, such as alignments, phasing, imputation, etc. The HPC facilities were not always reliable in terms of uptime, or we had low priority in the queue. Having said that, despite CHPC going down periodically for upgrades or maintenance, they were very helpful in providing support and extra time on their cluster. Transferring the data took a long time and had its challenges. We also had to ensure our alignment pipelines were identical for the different datasets, which took a lot of testing on different platforms. Trying to merge high and low coverage data is still an unsolved challenge. These are just some of our earlier challenges. Later we had a few challenges with the design information provided by the company, which could have been avoided with better communication. 🌍

*“The mystery of life isn't a
problem to solve, but a reality
to experience.”*

- Frank Herbert



The Growth of H3Africa

by JP Maree

In 2006, during the annual conference of the African Society of Human Genetics (AfSHG) in Addis Ababa, Ethiopia, the first steps towards the African genomics revolution were taken. Conceived from a partnership between AfSHG, the Wellcome Trust, and the National Institutes of Health, the Human Heredity and Health in Africa (H3A) Initiative was announced during a press release in London, June 2010. Founded on the vision of establishing research infrastructures to catalyse genomic and epidemiological research in Africa, with the ultimate aim of improving the health of African populations, H3A officially launched in 2012. Although there are several research capacity building initiatives in Africa, the H3A Consortium is unique as it involved Africans during the development phase, includes more countries than most other initiatives, has a great diversity of scientific interests, and a distinct focus on addressing important scientific questions through genomics. “The diversity of scientific interests in H3A is unusual and is a major strength as well as a challenge,” said Dr Jennifer Troyer, the H3A program director for the NIH.

While numerous obstacles were overcome to create the required research infrastructure, some practical and logistical challenges are still being faced by H3A researchers, like exorbitant shipping costs, obtaining institutional review board approval, the 2015 Ebola outbreak, political unrest, and strikes leading to university closures and internet

blocks, to name a few. Another challenge is the extra costs African scientists must bear when ordering reagents or laboratory equipment, which results in African scientists paying more than their European and American colleagues. “It’s scandalous given that the need is to build the science base on the continent, but African scientists are being surcharged as they develop their labs,” says Dr Audrey Duncanson, a Wellcome Trust senior portfolio developer. A sustainability plan will need to be developed to increase local support and funding. With the changing global climate, it is imperative to turn to local funders and donors. “The person with the money can drive the research agenda; they can develop questions and research relevant to their environments,” said Prof Charles Rotimi, Director of the Center for Research on Genomics and Global Health at NIH and a founding member of H3A who has been instrumental in its success.

Despite these challenges, the H3A Consortium has made tremendous strides in disease research, capacity building and resource development. Before the inception of H3A, inter-African collaborations were minimal. “African scientists were not talking to each other; H3A has created an umbrella body across the continent,” said Prof Rotimi. This has since changed enormously and is one of the huge successes of H3A, evidenced by the development of cross-H3A collaborative groups for cardiovascular disease, kidney disease and sickle cell disease, amongst others.

The H3A Consortium has grown from a tentative idea to a community of scientists who



work together for common goals. Some of the notable changes precipitated by the H3A Initiative are the cultural and collaboration reforms taking place in African research, with marked changes observed in the biomedical fields.

Another surprising development was the (unexpected) growth of the H3A trainees (known as the H3A Fellows), who went from being barely involved to becoming a vital and vibrant part of the larger community. “Initially, the young investigators were not very assertive. Now the young people are going beyond the research questions that PI’s initiated! I am very proud of all the H3Africa Fellows,” said Prof Rotimi. According to Dr Audrey Duncanson “The growth of the trainee group and the quality of the students that are coming through as PhD students and young researchers may be H3Africa’s most lasting legacy.”

H3A has been instrumental in empowering genomic research on both communicable and non-communicable diseases in Africa, with the evaluation of human genetic variation being particularly exciting. Although most of the findings have yet to be reported, valuable insights are being provided as to why Africans display varying susceptibility and progression of HIV, a higher risk of developing chronic kidney diseases, type II diabetes, stroke, heart disease, risk of obesity, as well as the impact of mental disorders on communities. Some projects are studying the distribution of the APOL1 gene variant and its role in chronic kidney disease in Africa, its effect on the

susceptibility to African sleeping sickness, and the epigenetic profile of trypanosomes. About 2.7 million previously unrecorded SNPs have been identified and are currently being used to create an African chip. The H3A network and infrastructure were perfectly positioned to help sequence the first Ebola virus strains and were instrumental in addressing the 2015 Ebola outbreak.

To assist H3A researchers with data analysis, a Pan African Bioinformatics network comprising of 32 bioinformatics research groups in 15 African countries, was established. Led by Prof Nicky Mulder at the University of Cape Town, H3ABioNet grants access to first class bioinformatics support and training, provides excellent resources to H3A scientists, and aids research projects through bioinformatics capacity development.

“I have enjoyed the growth of H3A. There was no way to anticipate how successful H3A was going to be!” said Prof Charles Rotimi. For Dr Audrey Duncanson “The most satisfying aspect is seeing the growth of a relatively small Consortium into something so large, and so cohesive and collaborative. Many H3A scientists refer to H3A as a ‘family’ and have a strong affinity with its aims and ambitions, I have never experienced that level of commitment to the collective in the many other genomics consortiums I have been involved in.”

H3Africa’s resounding success delivered way beyond initial expectations, created opportunities for biomedical research across



the continent to become a global enterprise, and enabled genomics to shape precision medicine and public health on the African continent. We thank Dr Audrey Duncanson, Prof Charles Rotimi, Dr Jennifer Troyer, and Dr Emmanuel Peprah for valuable insights into the founding and operations of H3Africa. 🌍

H3Africa Collaboration with the Online Community Engagement Platform *MESH* by Georgia Bladon

Successful implementation of genomic studies through H3Africa requires that communities are properly engaged on H3Africa's objectives and that any key issues are identified and addressed. To establish a community of practice that can address the key issues, members of the H3Africa Community Engagement Working Group have been working with the online initiative MESH to build on and share learning experiences from the Consortium's community engagement work so far.

MESH is a collaborative, open-access web space for people involved in community engagement with health research in low- and middle-income countries (LMICs). It provides an online meeting place where community engagement practitioners, researchers, health workers, funders, and others can network, share resources and discuss good practice. The site has over 450 members, is used in 121 countries, and hosts 70 resources including project reports, academic literature, funding advice, and practical tools to aid the creation

of high-quality engagement that has a real impact.

MESH is collaborating with the H3Africa Community Engagement Working Group to capture and map community engagement activities taking place across the Consortium, a resource which we hope will be useful across H3Africa and beyond. MESH will also host a suite of resources and reports emerging from two key community engagement workshops which took place in March 2017: The Wellcome Trust International Engagement Workshop "It's Complicated: Navigating Complexity in engagement" (6-8 March 2017) and the MESH Evaluating Engagement Workshop (9-10 March 2017).

The latter, organized and funded by MESH in collaboration with the Global Health Bioethics Network, was an opportunity for partners across large health programs working in LMICs - including H3Africa - to come together for an in-depth look at how community engagement can be effectively evaluated and the learning from that evaluation shared. Feedback on the workshop was very positive, and we hope that the knowledge captured from it will be useful to a much wider community.

If you are currently evaluating your community engagement work at a project or program-wide level, have a look at the available resources and the MESH evaluation map for assistance in choosing the appropriate evaluation approach and guides on how these approaches can be implemented at mesh.tghn.org/evaluation/. MESH encourages contributions and feedback. If you are involved in community engagement



in any capacity, visit the site, become a member, and join in on the learning! 🌍

Developing African

Biorepositories by Samuel Kyobe

On the 5th Anniversary of the founding of the Wellcome Trust-NIH H3Africa Program, we celebrate the growth and development of the H3Africa regional biorepositories. To demonstrate this growth, and facilitate the global gain in footprint, the program staff from Nigeria, South Africa, and Uganda developed six manuscripts, which have been accepted for publication in 'Biopreservation and Biobanking,' an official journal of the International Society for Biological and Environmental Repositories (ISBER). The manuscripts summarize the processes, experiences, and lessons learned by the biorepositories and will form a body of knowledge for the scientific community in LMICs.

"I'm very pleased that the H3Africa project leadership and researchers chose to publish a series of excellent manuscripts in our journal. I'm particularly excited that these papers will comprise a special section in our 15th-anniversary issue. Thanks again for sharing this important work with our readership!" said Jim Vaught, Editor-in-Chief of Biopreservation and Biobanking. The articles published in the April 2017 Anniversary Issue of 'Biopreservation and Biobanking' includes:

H3Africa Biorepository Program: Supporting Genomics Research on African Populations by

Sharing High Quality Biospecimens (Abimiku et al.); This serves as the Biorepository Program marker paper.

Genes for Life: Biobanking for Genetic Research in Africa (Mayne et al.); Defines the boundaries within which H3Africa established the biorepositories and describes challenges and gaps to be filled by H3Africa regarding biobanking in Africa.

Accessing Biospecimens from the H3Africa Consortium (Beiswanger et al.); This article describes the H3Africa Biospecimen access policies that will enable sharing of the accrued samples worldwide. Key questions of commercialization, custodianship, and co-operation within the African context are articulated in the policies. A template MTA developed with consortium-wide consultation is provided to facilitate biospecimen access.

Lessons Learned from Biospecimen Shipping amongst the Human Heredity and Health in Africa (H3Africa) Biorepositories (Croxtan et al.); The biorepositories conducted a pilot study to assess the ethical and logistical conditions required for sharing biospecimens on the continent. The pilot study assessed the impact of these conditions on the quality of biospecimens with attendant lessons and recommendations.

Selecting a Laboratory Information Management System for Biorepositories in Low and Middle Income Countries: The H3Africa Experience and Lessons Learned (Kyobe et al.); This paper provides an insight into the steps that were taken by the three biorepositories to



choose a LIMS. The article covers a list of requirements that should be met by a LIMS vendor before choosing the software.

The lessons learned and alternative approaches are discussed for LMICs.

Baobab LIMS: Development of an open source LIMS for Biobanking (Bendou et al.); Describes the development and scope of BIKa LIMS - an



The H3Africa Program funding culminated in a visit by the NIH Director, Dr. Francis Collins, to Uganda on 5th & 6th August 2016, during which he officially opened the Integrated Biorepository of H3Africa Uganda.

Fogarty Emerging Global Leader Award

by Laura Povlich and Barbara Sina

The Fogarty International Center at the NIH has an open call for applications for the Fogarty Emerging Global Leader Award. This award aims to provide research support and protected time to research scientists from LMICs who hold junior academic faculty positions or research scientist appointments at LMIC academic or research institutions. Applications are invited from LMIC research

scientists from any health-related discipline, including genomics, who propose both critically needed career development activities and a research project that is highly relevant to the health priorities of their country. Candidate career development plans must include mentorship by at least one U.S. and one LMIC mentor and can include activities at U.S. institutions or other sites. Examples of currently funded awards are described in Fogarty's Global Health Matters newsletter. Applications for the Fogarty Emerging Global Leader Award are due December 14, 2017 and should be submitted to the NIH through instructions in the funding opportunity announcement and Grants.gov. More information can also be found on the program page, which includes answers to Frequently Asked Questions. Additional questions should be directed to the Program Officer, Christine Jessup, at Christine.Jessup@nih.gov.

Individuals who are interested in updates on this opportunity and other Fogarty International Center funding opportunities should subscribe to Fogarty's weekly Funding Newsletter. 🌍

Global Health Matters Newsletter:

www.fic.nih.gov/news/pages/2016-emerging-global-leader-k43-awards.aspx

Funding Newsletter subscription:

<https://public.govdelivery.com/accounts/USNIHFIC/subscriber/new>

Emerging Global Leader Award (K43) Funding Opportunity Announcement: <https://grants.nih.gov/grants/guide/pa-files/PA-17-001.html>

Emerging Global Leader Program Page: www.fic.nih.gov/Programs/Pages/emerging-global-leader.aspx



The 9th H3A Consortium meeting: Graced by a special guest

by Tafadzwa Machipisa

With the goal of improving the health of African populations, the H3Africa Consortium is a pioneering initiative which aims to facilitate a contemporary research approach to the study of genomics and environmental determinants of common diseases in Africa. The consortium consists of African and international researchers, trainees who are Fellows, as well as corporate and governmental collaborators all working towards developing and implementing innovative research.

The consortium began in 2012 and holds two meetings a year, usually in a country on the African continent. In the past, meetings have taken place in; Ethiopia (Addis Ababa), Ghana (Accra), Senegal (Dakar), South Africa (Johannesburg and Stellenbosch), Tanzania (Dar es Salaam), Zambia (Livingstone), and in October 2015, the consortium was treated to a meeting in Washington (D.C., USA). The 9th H3Africa meeting took place during October 2016, on the warm and vibrant island of Mauritius, at Le Meridien. A diverse group of 12 H3Africa Fellows from different African countries were awarded travel grants, funded by the NIH and the Wellcome Trust, to attend this meeting. The travel grant awardees were expected to present their research and take part in activities at the consortium.

The 9th H3Africa Consortium meeting marked the first H3Africa meeting to be attended by the hosting nation's president. Her Excellency,

Dr Ameenah Gurib-Fakim, graced us with her presence as she opened the meeting proceedings on the 29th of October. Through sharing her knowledge, Dr Gurib-Fakim encouraged African governments to increase their investment in STEM (science, technology, education and mathematics).



Her Excellency, Dr Ameenah Gurib-Fakim, delivering her opening speech at the 9th H3Africa Consortium meeting at Le Meridien, Mauritius.

Proceedings of the meeting took place as follows:

Day 1: On the 27th, the Genome Jamboree and literature review workshops were held,



concurrently. These helped Fellows hone their research methods and writing skills.

Day 2: On the 28th, the Fellows Research Day was held at the University of Mauritius. Selected Fellows orally presented their research work in 8 minutes, competing for awards that were received by the top three presenters.

During the evening, a mentorship session was held. The mentors (Prof Enoch Matovu, Prof Clement Adebamowo, Prof Samar Kamal, Dr Victoria Nembaware and Dr Jennifer Troyer) spent some time having a Q&A session with the Fellows. The common questions raised by Fellows were themed around data ownership and sharing, and career development (with personal examples being shared by the mentors).

Day 3: On the 29th, the meeting was opened by the Mauritian presidential address. Following the opening speech, the PI presentations session were hosted. Furthermore, during the breaks, the H3Africa Fellows presented their posters, which were reviewed by judges. Subsequently, that evening the Fellows Awards were presented during the dinner.

Day 4: On the 30th, the Working Group Day was held. The Working Groups in H3Africa are the respective arms of the H3A projects as they look into areas of development and map the future of the consortium projects. Chairs of the Working Groups report the progress of the groups bi-annually at the H3A meetings. At the 9th Consortium meeting, a few Fellows were

fortunate to join in on the sessions by invitation of the respective Working Group Chairs. Later that afternoon, there was an optional social excursion outside of the meeting on the catamaran. Everyone had an opportunity to socialise in mixed groups, including, PIs, funders and Fellows alike, in a relaxed atmosphere. There was also some fun, team building activities such as boat dance battles as the sun set. The highlight of the evening was driving through the “Festival of Lights- Diwali”, on the way back to dinner. The dinner at the hotel was graced by dancers on the beach celebrating Diwali (a local holiday).

Day 5: On the 31st, the HIV/AIDS Comorbidity Meeting was held, which concluded the consortium. This was a new addition to the meetings, to accommodate research that emerged from the HIV pandemic.

In conclusion, the Fellows would like to thank the funders, judges and reviewers of our research, the senior researchers who provided mentorship for the Fellows. A special mention to the organisers who helped the Fellows' activities to be fun, fruitful, and educational! 🌍



Training Corner by the ECTWG

In this edition of the H3Africa Newsletter, the training corner is highlighting some achievements by the H3Africa Trainees. Congratulations!

Julius Mulindwa (TrypanoGen Project):

Dr Julius Mulindwa is a postdoctoral researcher studying African trypanosomiasis at Makerere University in Kampala, Uganda. Mulindwa was awarded one of the American Society of Tropical Medicine and Hygiene's (ASTMH) 2016 Annual Meeting Travel Fellowships. You can access his interview on the Global Now website.

Rehab Ahmed (H3ABioNet Consortium):

Rehab from CBSB, University of Khartoum, was recently awarded a Research Development Grant from the Wellcome Trust Brighton and Sussex Centre for Global Health Research to work on the wet-lab based part of her PhD research. She is currently working with Dr Simon Waddell on screening lipid interfering molecules for their anti-TB potential at the Brighton and Sussex Medical School.

Charlotte Osafo and Yemi Raji (Kidney Research Project):

Charlotte and Yemi were recently accepted into a prestigious Master's Degree Program in Human Genetics at the University of Michigan, Ann Arbor. This achievement was highlighted by Dr Francis Collins, the NIH Director, in his blog.

Dr Emile Chimusa (H3ABioNet):

Was offered a permanent position as a Senior Lecturer in the Division of Human Genetics at the University of Cape Town where he is establishing a Computational Population Genetics Group. Such positions are rare and highly competitive!

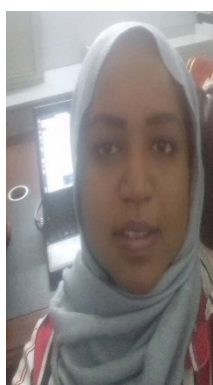
Dr Sumaya Mall (Schizophrenia):

Was offered a permanent position as a Senior Lecturer in the School of Public Health at the University of Witwatersrand, Johannesburg.

(Please send us your achievements or awards for inclusion in this section!)



Julius Mulindwa



Rehab Ahmed



Charlotte Osafo



Yemi Raji



Emile Chimusa



Recent Publications from the Consortium

2016:

Controlling cardiovascular diseases in low and middle income countries by placing proof in pragmatism; Owolabi et al. PMID: 27840737

National ethics guidance in Sub-Saharan Africa on the collection and use of human biological specimens: a systematic review; Barchi et al. PMID: 27770794

2017:

Regulation of genomic and biobanking research in Africa: a content analysis of ethics guidelines, policies and procedures from 22 African countries; de Vries et al. PMID: 28153006

"I passed the test!" Evidence of diagnostic misconception in the recruitment of population controls for an H3Africa genomic study in Cape Town, South Africa; Masiye et al. PMID: 28202021

Exploring Overlaps Between the Genomic and Environmental Determinants of LVH and Stroke: A Multicenter Study in West Africa; Adeoye et al. PMID: 28302552

Stark Regional and Sex Differences in the Prevalence and Awareness of Hypertension: An H3Africa AWI-Gen Study Across 6 Sites in Sub-Saharan Africa; Gómez-Olivé et al. PMID: 28302553

Development of Bioinformatics Infrastructure for Genomics Research in H3Africa; Mulder et al. PMID: 28302555

Prevalence and Prognostic Features of ECG Abnormalities in Acute Stroke: Findings From the SIREN Study Among Africans; Adeoye et al. PMID: 28302557

Well-positioned nucleosomes punctuate polycistronic pol II transcription units and flank silent VSG gene arrays in *Trypanosoma brucei*; Maree et al. PMID: 28344657

H3Africa Biorepository Program: Supporting Genomics Research on African Populations by Sharing High-Quality Biospecimens; Abimiku et al.

Genes for Life: Biobanking for Genetic Research in Africa; Mayne et al.

Accessing Biospecimens from the H3Africa Consortium; Beiswanger et al.

Lessons Learned from Biospecimen Shipping Among the Human Heredity and Health in Africa Biorepositories; Croxton et al.

Selecting a Laboratory Information Management System for Biorepositories in Low- and Middle-Income Countries: The H3Africa Experience and Lessons Learned; Kyobe et al.

Baobab Laboratory Information Management System: Development of an Open-Source Laboratory Information Management System for Biobanking; Bendou et al. PMID: 28375759

Neurological Complications in Subjects With Sickle Cell Disease or Trait: An Observational Study From Mali; Landouré et al. PMID: 28377104

Cohort Profile: African Collaborative Center for Microbiome and Genomics Research's (ACCME) Human Papillomavirus (HPV) and Cervical Cancer Study; Adebamowo et al. PMID: 28419249

Giving voice to African thought in medical research ethics; Tangwa 2017. PMID 28343255