Can you provide a brief history of the International Rare Diseases Research Consortium (IRDiRC) and how it was formed?
The initial conversation that ultimately led to the formation of IRDiRC took place in 2009 between Dr Ruxandra Draghia-Akli of the European Commission (EC) and Dr Francis Collins of the US National Institutes of Health (NIH). Both parties identified a need for greater international collaboration and increased attention from funders in the area of rare disease (RD) research. They also recognised the huge opportunity provided by developments in next-generation genome sequencing technologies, and believed that the formation of an international consortium of research funders could encourage closer collaboration and attract higher levels of funding. In October 2010, the EC and NIH held the first of three preparatory workshops that led to the formation of IRDiRC. Now, the Consortium comprises 40 public and private sector members from 16 countries, who have collectively committed approximately US $2 billion to research RDs, and three invited patient advocacy groups.

How did you become Chair of IRDiRC, and what are your main responsibilities within this role?
Since 2010, I have been Scientific Director of the Institute of Genetics, a constituent institute of the Canadian Institutes of Health Research (CIHR). Canada has a longstanding strength in RD research, and in 2011 CIHR joined IRDiRC as one of its early funder members. In the following year, my colleagues on the IRDiRC Executive Committee selected me to become the chair, with my term beginning in April 2013. I consider it particularly important to work on expanding the Consortium’s membership, to make IRDiRC an increasingly visible organisation in health research, and to facilitate the achievement of initiatives that are developed by our scientific committees.

Is the Consortium on track to meet its targets of delivering 200 or more new therapies by the end of the decade and improving RD diagnostics?
IRDiRC has tabulated 137 new RD therapeutics that have received European Medicines Agency (EMA) or US Food and Drug Administration (FDA) approval since 2010, so we appear to be on track. The situation with diagnostics is more complex. If there are (as estimated) 7,000 RDs, then the present rate of discovery is not fast enough for all RD diagnostics to be identified by 2020. But there is some uncertainty about how many RDs there actually are. On the one hand, new diseases

E-RARE-3
In recent years there has been increasing interest among funding agencies to finance rare disease projects. One notable example is the extension of ERA-Net (an EC scheme to increase collaboration) ‘E-Rare’ to a third phase (2014-2019). It aims to implement the objectives of IRDiRC and support Europe’s rare disease research efforts.
The present funding call from E-Rare-3 brings together 23 different funding organisations from 17 countries, in partnership with the European Commission, to support multilateral translational research projects in rare disease. To find out more visit www.erare.eu.
are regularly being discovered, especially as awareness about RDs increases worldwide. On the other hand, some patients who were thought to have an uncharacterised disease have turned out, upon sequencing of their genome, to have two known diseases, or to show an atypical presentation of a known disease, potentially reducing the overall number.

Can you describe the main obstacles IRDiRC has faced in the realm of RD research?

Most of the genetically based RDs with unknown causative genes – and thus which lack a diagnostic – have extremely low prevalence rates. A key strategy towards identifying the causative mutation for a given disease is to identify a genetic variant that is shared among the affected individuals but is absent among unaffected individuals. We are using genomes from unaffected individuals that have been sequenced in large-scale projects such as the 1,000 Genomes Project to make these comparisons. This strategy becomes less effective as patient numbers decrease, and is seriously weakened if only a single patient is available.

How is the Consortium striving to overcome these challenges?

A major tool we are using is collaboration. IRDiRC’s efforts to foster better international collaboration are enabling researchers with unsolved patients to search for other unsolved patients with similar phenotypes in the databases of other researchers, allowing the causative genes for some of these ultra-rare conditions to be discovered.

In which ways is the Consortium helping to achieve the global RD research community’s core objectives?

In addition to the substantial funding for research provided by its members, IRDiRC strives to facilitate progress towards these objectives by supporting the development of methods for researchers to query each other’s genomic and phenotypic data, to enable collaboration while maintaining patient privacy.

Furthermore, IRDiRC is supporting the establishment of a standardised consent language that is internationally recognised and would better enable data sharing. We have also had successes on the therapeutic side. In August 2014, the EC granted the market authorisation of ataluren – an innovative drug developed to treat patients with nonsense mutation Duchenne muscular dystrophy – to the IRDiRC member PTC Therapeutics. Additionally, in 2013 the FDA approved mipomersen, a drug developed by Isis Pharmaceuticals in partnership with Genzyme (both IRDiRC members) to treat patients with homozygous familial hypercholesterolemia.
ANALYSIS

Would you say that RD research is driving innovation?

RD research is a key innovation driver. The diagnosis of RDs is a large impetus for the clinical introduction of whole-exome or whole-genome sequencing, which is now in place in numerous centres in the US, Europe, Canada and beyond. Furthermore, many RD therapeutics based on innovative technologies such as gene therapy, cell therapy, exon-skipping, stop codon readthrough and antisense ribonucleic acid are in clinical trial, and some therapies of this type are beginning to receive market authorisation. RD research is also driving necessary changes to clinical trial design, which makes trials maximally informative when patient populations are very small.

Where have the Consortium’s key successes come from to date?

IRDiRC’s key successes include the rapid growth of the organisation and the aggregate funding commitment of its members. In collaboration with the Global Alliance for Genomics and Health (see page 6), the Consortium is facilitating responsible sharing of genotypic and phenotypic data and developing international standards for patient consent.

Once the 2020 targets have been achieved, how do you envision IRDiRC moving forward?

There will be a great deal of work to do beyond 2020, even if IRDiRC’s two key objectives are fully met. Many RDs will not have an effective therapy, and many RD patients throughout the world will still lack access to the most advanced diagnostics and therapeutics. I envision that IRDiRC or a successor organisation will have a continuing role in ensuring that RD research receives the high priority it deserves within the global health research effort.

www.irdirc.org

RARE DISEASES: THE FACTS

The European Commission defines a rare disease (RD) as a disease that affects fewer than 1 in 2,000 individuals

While in the US an RD is defined as affecting fewer than 200,000 of its citizens – roughly 1 in 1,500 people

Collectively, RDs are quite common. There are approximately 7,000 of them in total

If every individual with an RD lived in one country, it would be the world’s third most populous country

RDs affect approximately 5% of the human population – as many as 350 million people worldwide

Approximately half of individuals affected by RDs are children – 35% of deaths from RDs occur in the first year of life

80% of RDs result from genetic variation, and can therefore affect individuals throughout their lifetime