**STAR-IDAZ** **Roadmaps for the control of helminth infections in ruminants**

**Background on STAR-IDAZ roadmaps**

The objectives and deliverables of the STAR-IDAZ research roadmaps are to coordinate research at international level to contribute to new and improved animal health strategies for at least 30 priority diseases/infections/issues.

Deliverables include:

* Candidate vaccines
* Diagnostics
* Therapeutics
* Other animal health products and procedures
* Key scientific information/tools to support risk analysis and disease control

The research roadmaps are

* A way of visualizing a complex problem
* Provide a structure and focus on where research is most needed, identifying bottlenecks and critical gaps
* Projects are mapped onto the gaps allowing us to determine which areas are being addressed and which require further research
* Provide a valuable resource for the research community including funders
* Interactive, ‘living’ tool publicly available online at www.star-idaz.net

**Graphical abstract**

**For a better**

***CONTROL***

**of helminth infections we need**

Therapeutics

Vaccines

Diagnostics

**Introduction**

Helminth infections have significant negative impacts on production efficiency in ruminant farming systems worldwide, and their effective management is essential if livestock production is to increase to meet future human needs for dietary protein.

The control of helminths relies on pasture management practices combined with the use of chemotherapeutics. Frequently, the dependence of chemotherapeutics is high and this approach is unsustainable as resistance to anthel­mintic drugs is widespread and increasing. At the same time, infection patterns are being altered by changes in climate, land-use and farming practices. Future farms will need to adopt more efficient, robust and sustainable control methods, integrating ongoing scientific advances.

In the present document the key priority research needs of the different roadmaps of helminth control in farmed ruminants are presented, bringing to bear the research needed in: (1) diagnostic tools, (2 vaccine development, (3) therapeutic developments and (4) the rational integration of future control practices. Rather than relying on the single option of anthelmintic treatment based on few anthelmintic drug classes, the future of helminth control should be based on an array of complementary control options that can be flexibly used based on the local farm management and helminth epidemiological patterns.

Scientific and technical advances will place new tools in the hands of animal health decision makers and allow them to achieve a more integrated and sustainable approach to helminth control in support of animal welfare and production.

The objectives of the present documents are thus:

* to present the key priority research needs forwarded by the members of the Helminth working group
* to prepare a draft research application to be submitted (to be determined where).

**Methodology**

Members of the Helminth working group were assigned by the Livestock Helminth Research Alliance (LiHRA) and developed the road maps with the support of the COST Action COMBAR.

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| **Sub-groups** | **Leaders & Vice Leaders** | **Participants** |
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The LiHRA was founded to address the current challenges of helminth control of livestock and stimulate collaborative research on the topic. The alliance comprises international partners with a recognised expertise in different disciplines applied to helminth research. LiHRA collaborates with STAR-IDAZ IRC to construct STAR-IDAZ roadmaps to coordinate future research and bring novel control solutions based on improved diagnostics, new therapeutics and vaccines to real life.

**Key priority research needs forwarded by the members of the Helminth working group**

**Diagnostics**

**1) Biomarker based tests for determining helminth infection intensities and impacts**

The accurate *in vivo* assessment of helminth infection intensities and clinical/welfare/production impacts using both pen-side and laboratory-based tests are urgently needed. Biomarkers secreted by live parasites (including inhibited stages) (e.g. proteins/peptides, metabolites, RNA molecules) that are present in host blood, saliva, milk or feces have significant potential as diagnostic biomarkers.

Research priorities include: (i) the identification of secreted stage-and species-specific proteins/peptides using immunological or proteomic technologies or the detection of small molecules/metabolites using mass spectrometry or chemical assays; (ii) validating these biomarkers for use in clinical trials, epidemiological and production impact studies.

**2) Identification and validation of molecular diagnostic markers for anthelmintic resistance.**

Molecular diagnostic assays that detect the frequency of drug resistance mutations in helminth populations are urgently needed as sensitive, accurate and scalable diagnostic markers for drug resistance. Challenges include the identification of the relevant drug resistance mutations, validation of their role in resistance and the development of appropriate diagnostic platforms.

Research priorities include: improving reference genomes of major parasite species of importance, applying population and functional genomics approaches to identify and validate resistance mutations as diagnostic markers and developing appropriate molecular diagnostic platforms, both laboratory and pen-side, to allow flexible and affordable molecular based diagnostic tests.

**3) Improving and automating microscopy-based helminth diagnostics**

Detecting parasite stages in feces and blood by microscopy is labor intensive and requires specialist expertise which makes it both expensive, difficult to standardize and often locally unavailable.

Research priorities include: development of more scalable, reliable, less labor-intensive and cost-effective systems for microscopy-based parasite detection for both pen-side and laboratory use. This includes of the use of artificial intelligence for automated sample processing and image analysis to generate automated detection and enumeration of parasitic elements.

**A cross-cutting priority across all three of the above areas is the development of pen side tests and associated decision support tools.**

**Vaccine Roadmap**

**1) Understanding protective immunity and variability in vaccine response between hosts**

Proof-of-principle exists for the vaccine-mediated protection of cattle and sheep against helminth infections, specifically gastrointestinal nematodes (GIN) and liver fluke. However, further research is necessary to fill knowledge gaps in two specific areas related to protective immunity. Although stakeholders may expect vaccines to have the same level of efficacy as anthelmintics in reducing parasite burdens, this may not be necessary for a successful vaccine to play a part in control programmes. Unfortunately, not all animals respond equally well to vaccination, and those which respond poorly represent a significant element of the flock/herd in which productivity remains low despite vaccination. These poor responders are also responsible for the continued contamination of pasture affecting naïve stock following lambing/calving. Identification of protective immune responses (from antigen recognition to effector responses), including why some animals respond well and others do not, will inform strategies for antigen discovery, antigen delivery and adjuvant selection. Another barrier to successful vaccination is reproducibility and it has been difficult to eliminate variability in protection levels in sequential trials against parasitic helminths, even when great efforts are made to avoid sources of variation.

In terms of GINs, with continuous ingestion of infective larvae, small ruminants develop an age-related natural immunity to worm infestations. This can manifest as a “self-cure” reaction which can eliminate other abomasal and intestinal nematodes. The expression of immunity in ruminants is consistent with a T helper 2 (Th2) response with production of sensitized CD4+ lymphocytes expressing and secreting interleukins IL5, IL13 and TNFα. That said, there can be subtle differences in the contribution of Th1 and Th2 responses in different hosts and to different nematode species, the key is to identify ‘protective’ immune responses. Resistance to parasitic nematodes in ruminants is associated with increasing levels of parasite‐specific IgG1, IgA, IgE, mucosal mast cells and eosinophils. These responses prevent parasite establishment, suppress egg production, and remove adult worms. One of the biggest challenges of vaccine development is trying to replicate this natural response in the definitive host.

In contrast, ruminants do not develop protective immunity to *F. hepatica* following infection, and remain susceptible for their entire lifetime. An effective vaccine, therefore, has to produce an immune response different from that of the natural immune response. There is substantial evidence that this parasite is capable of downregulating immune responsiveness, both to itself and to other pathogens. Natural infection induces a Th2/T reg response, with IgG1 as the dominant antibody subtype. There is some evidence that vaccines which induce a more balanced Th1/Th2 response, with good levels of parasite-specific IgG2 as well as IgG1, can be protective, and that the affinity of the antibody response for target antigens is important. Most antigens that have shown some effect to date have been secretory antigens. There is some evidence that glycan (carbohydrate) moieties on both structural and secreted fluke antigens are important in directing the host immune response, and this is likely to become a major focus of fluke vaccine research. Finally, there is also evidence that some immunodominant epitopes on major candidate antigens are “decoy” antigens, and smart vaccines which do not contain these epitopes may be developed to allow the immune system of the host to “find and destroy” key protective epitopes. Studies of host transcriptomic responses to infection are yielding clues as to how the parasite manipulates the host immune system, and may provide evidence as to which adjuvants, as well as antigens, will be most useful in next generation fluke vaccines.

1. **Expressing effective recombinants**

Multiple trials with helminth parasite extracts have shown that high efficacy may be achieved using “native” antigens i.e. extracted directly from parasite material, but this is rarely a practical option for commercial vaccine development. A better approach would be through the use of recombinants which mimic the highly protective native molecules/complexes. There has been very little success so far with single recombinantly-derived vaccine antigens, expressed in conventional expression systems (*E. coli*, insect cells, *Pichia*), however, cocktails of different antigens have been shown to provide improved protection. The challenge then becomes to refine antigen production to the minimum number required to provide sufficient and consistent protection. Based on an antigen's conformation and secondary modifications (e.g. glycosylation), flexible, modifiable expression systems may be needed.

Other efforts in this sphere are focusing on understanding glycosylation pathways in parasitic helminths, and the resultant glycoproteins expressed. Synthetic biology to allow appropriate sugar residues to be added to protein scaffolds is a promising strategy for advances in this area.

**3) Can we develop a polyvalent vaccine that gives long-lasting protection against mixed species infections?**

There are very few circumstances where control of a single nematode species would be adequate for commercial success of a vaccine, the exception to this probably being Barbervax in certain areas of Australia (mainly because *Haemonchus* is so dominant and pathogenic). Polyvalency in nematode vaccines is, therefore, likely to be highly important for a number of reasons including the following: The effects on production imposed by GIN are the result of multi-species infections. Vaccines which target single species may be compromised in their efficacy if the remaining species are pathogenic and especially if the remaining species produce immunomodulators which may negatively influence the effectiveness of the vaccine against the target species. Producing a single vaccine with efficacy against both a range of nematodes and liver fluke is a long-term goal, given the other barriers to be overcome initially. However, there is typically a great deal of variability within helminth parasite populations, which, in addition to natural host variability in immune response, has been an issue in ensuring consistent vaccine performance. To this extent, examining the degree of genetic variability within candidate vaccine antigens will be an important step in ensuring protection against all common helminth variants. To this extent, a single helminth vaccine may require this aspect of “internal polyvalency”. It is possible that effective liver fluke vaccines will also contribute to the control of rumen fluke infections, which are an emerging disease problem in Northern Europe, provided such vaccines demonstrate some cross-protection against the two fluke species.

**Improved therapeutic response against helminth parasites in ruminants**

**1) Search for approaches to achieve improved therapeutic response for existing anthelmintics in livestock animals**

In cases where existing anthelmintics still show moderate to high efficacy, there efficacy can be maintained or improved by strategies based on enhanced drug exposure, drug combinations and the use ofbioactive natural products. Further experimental work is needed to confirm if the observed therapeutic benefits can be used under field conditions. This is particularly relevant for cattle nematodes, where we still have some efficacious tools within the existing anthelmintic drugs and/or their combined use to expand the spectrum/efficacy.

**2)  Identification of novel active pharmaceutical and/or phytochemical ingredients (API) with alternative mode of action.**

Genomic-assisted drug discovery and/or other screening-based technologies should be supported to come up with some novel molecules active against multi-resistant helminth parasites.  The elaboration of a target product profile (TPP) for new API with anthelmintic activity will guide the assessment of the clinical efficacy and safety in the process of development of any potentially new compound.

Further epidemiological, genetic and pharmaco-parasitological based research to understand the mechanisms of resistance in different helminth parasites of economic relevance in livestock animals is required. This information will be critical to define a “rational use” for any novel API introduced into future helminth control programs.

**Control strategies (Nematodes)**

**1) Research on the mechanisms used by different host species and possibly breed to avoid, control or expel their GIN infection, including immune resistance, innate responses and resilience.**

A crucial research target is to recognise the mechanisms used by animals to avoid, control and expel their gastrointestinal nematodes (GIN) infections and to identify why specific individuals within a group have high worm burdens and thus contribute mostly to further infections of the whole population. If we know that most animals have low worm burdens and very few have high worm burdens, then it is essential to either identify those mechanisms used by the majority of animals to avoid, control and expel their GIN infections or identify those animals that have high burdens and thus contribute mostly to further infections. When these aspects are better understood we must also look at how these mechanisms are further affected by feeding behaviour, grazing management options, nutritional manipulation, nutraceutical plants or different anti-parasite vaccines and their relationship with gut microbiota and how these mechanisms can be exploited through breeding for disease resistance.

The combination of worm resistant animals, correct nutritional manipulation and vaccines may substantially reduce the need for AH treatments to the point where their primary function is to provide therapeutic treatments rather than their current role which is mostly prophylactic. Funding should be targeted for different laboratories willing to work and collaborate on immune mechanisms in sheep, goats, cattle and horses and should include the exploration of phenotypic results with genotyping, transcriptomic and proteomics.

**2) Improving risk assessments (modelling, production impacts) leading to better decision support tools for the targeted use of different control methods in a sustainable integrated control approach**

It is essential to generate “big data” from farmers, vets and other stakeholders that may improve our understanding of the risks associated with GIN in different grazing ruminant production systems, under different ecological zones. The continuous production of data can be generated by mobile phone applications, websites or any new mobile device, which can generate "big data" (within accessible, large scale databases) from stakeholders on disease events, production impact, and costs of conventional or non-conventional treatments. When incorporated into models the latter will also help us to understand the effects of climate change on GIN problems worldwide, allowing better prediction of future disease challenges for a particular environment and timely interventions to be made.

Mechanistic (process-based) models have a key contribution to make to predicted risks under climate change, since purely data-driven approaches are limited to conditions already experienced. Together, these approaches will ultimately help us to design better decision support tools for different control methods, which can be used by farmers or other stakeholders. The users may also help with their feedback on their results to improve the accuracy of the advice.

**3) Studies on the integration of different control options for different species and genotypes of ruminants under different socioeconomic and environmental conditions, aiming to generate locally valid “good parasite management” practices.**

A worldwide network of researchers should be in charge of investigating the integrated use of control methods in different ruminant species under different climatic conditions. All these projects must choose several available control options and apply them within their relevant production systems to validate the success of those interventions leading to locally valid "good parasite management" practices. The results from different groups could be documented and the information could be shared at local levels to stimulate other farmers and vets to adapt and adopt integrated parasite control management. All the groups must perform their studies following harmonization guidelines or “best practice” advice professionally adapted to test the different GIN control methods. The latter could help researchers of different laboratories (Governments or Universities) around the world to make a correct evaluation of the different integrated methods, for example, adapted methods of grazing management, targeted selective treatments or dietary interventions. The availability of such guidelines/best practice advice could also help the publication of results that followed those methodologies.

Reintroduction of susceptible nematode species is one way to reduce the level of anthelmintic resistance on-farm. Each country should also be in charge of finding and maintaining GIN isolates with susceptibility to all conventional AH classes. The susceptibility of these isolates must be confirmed through standardized phenotypic *in vitro* tests and genetic markers/tools. For this purpose, it will be important to fund certified regional/national/international laboratories that can warrant the identification, production and preservation of those AH susceptible isolates. These centres would also greatly facilitate experimental studies on different control approaches. Resistance reversion must rely on isolates that are innocuous for the farm in terms of viruses and bacteria. The isolates found and characterized in each region of the world could be preserved in one or more internationally funded laboratory that act as reference laboratories.

**4) Implement socioeconomic studies to quantify the effects of control methods leading to their optimal use under different scales, geographies and production types aiming to ensure the sustainability of farmers and anthelmintic control business models.**

The application of different GIN control methods, or combination of methods, should consider the need to maintain the business models of the different relevant methods to ensure long-term sustainability. Those businesses will be in charge of producing the diagnostic and control tools and providing the necessary advice for the adequate use of the control tools. On the one hand, all the GIN management at the farm level, including decision-making tools (diagnosis) and the different control methods used, must be cost-effective for farmers, environmentally friendly and promote the welfare of animals. Thus, there is a delicate balance between the provision of cheap and reliable control tools for farmers on the one hand, and on the other hand the need for maintaining healthy business models producing the control tools. Thus, all stakeholders involved in GIN control must be allowed to maintain their business while they respect their customers. Without this, many control methods will not be available for farmers, including for example commercial anthelmintics, nematophagous fungi, anti-worm vaccines, animal feeds with nutraceutical materials or copper oxide needles. The necessary socio-economic analyses should warrant a fair and healthy business environment for farmers, vets and other stake-holders. This may be aided through low-cost access to diagnostics or advice from practitioners. In such cases the cost/benefit analysis for justification must also include assessment of the benefit to the entire community considering the one health principles and the key role that animals have in the social fabric of different societies in providing nourishment and food security.

**Control Strategies (*Fasciola* spp.)**

**1) Research on host mechanisms to avoid / control / expel *Fasciola* infection**

Immunity to *Fasciola* in grazing livestock is less effective than against nematodes. There is some evidence for resistance to reinfection in cattle, although the mechanisms are poorly understood. Candidate vaccines have been developed but protection so far is inconsistent. Research into host responses to infection should include but expand beyond immunology and consider physiological (e.g. fibrosis) and behavioural (e.g. avoidance of high risk pasture) mechanisms, as well as variation within and between host species and breeds and its genetic basis. This could provide routes to selection of livestock better suited to production on high risk pastures, with less reliance on chemical intervention.

Susceptibility to infection in the intermediate hosts also requires more attention: host range and switching, and disparities in cercarial production between *Galba* spp. strains, suggest that the dynamics of infection in the intermediate host is more changeable than previously supposed, and could provide routes to new management tools.

**2) Improving risk assessments (modelling, production impacts, TST) leading to better decision support tools for the targeted use of different control methods in a sustainable integrated control approach**

It is essential to generate “big data” from farmers, vets and other stakeholders that may improve our understanding of the risks associated with *Fasciola* spp. in different grazing ruminant production systems, under different ecological zones. The continuous production of data can be generated by mobile phone applications, websites or any new mobile device, which can generate "big data" (world-wide database) from stakeholders on disease events, production impact, and costs of conventional or non-conventional treatments. When incorporated into models the latter will also help us at understanding the effects of climate change on *Fasciola* spp. problems worldwide allowing better prediction of future disease challenges for a particular environment and timely interventions to be made. It will ultimately help us to design better decision support tools for different control methods, which can be used by farmers or other stakeholders. The users may also help with their feedback on their results to improve the accuracy of the advice. For *Fasciola*, better reporting of liver lesions form abattoirs is within reach and could provide datasets for evaluation of risk, as well as direct feedback to farmers on the effectiveness of control. Mechanistic models that take account of climatic, geographical and management influences on disease risk are called for, to be used alongside data-driven approaches to predict changing risks and appropriate responses under climate change.

**3) Combining strategies for integrated, sustainable control of *Fasciola hepatica***

Relatively few products are effective against *Fasciola* spp. and while their efficacy against the different stages/ages varies, triclabendazole stands out, with high efficacy against all stages. However, resistance to this compound occurs globally and there are reports of resistance to two other classes also, namely closantel and albendazole. In the face of increasing fasciolicide resistance, better knowledge of how to preserve the efficacy of existing products is required. For example, better utilization of each drug’s spectrum of efficacy against different stages of fluke, whether drug classes should be rotated in an attempt to preserve susceptible parasites within a population and how to combine management and drug prophylactic programmes. Evidence to support management options for fluke control, to reduce reliance on chemotherapy is an urgent research need.

Research is needed to evaluate the efficacy of management measures such as avoiding contaminated pasture at high-risk times of year, survival of infective metacercariae on pasture and in stored forages and strategic treatments to reduce contamination of pasture. Mathematical and epidemiological models informed by carefully designed field studies to collect data are needed, supported by evaluation of the sustainability of each method, viz-a-viz effect on selection for drug resistance.Over-reliance and extensive use of drugs are likely to lead to the emergence and spread of resistance, hence the development of programmes that preserve and maximize the efficacy of current drugs is a research priority. Since *Fasciola* is a highly pathogenic parasite, targeted selective treatment-type systems for more sustainable anthelmintic efficacy pose risks in leaving a proportion of a group of animals untreated. In addition, in contrast to GINs, both *Fasciola hepatica* and *F. gigantica* are ubiquitous parasites whose life cycles include a biological intermediate host, with some reservoir in wild life. Both species are also potential zoonotic agents. Hence a better understanding of the principles behind refugia-based control programmes is needed for fluke, based on knowledge of the underlying principles behind refugia, including how resistance genes flow within populations of fluke. For these experiments, a combination of *in vivo* experimental studies and genetic markers for resistance, are needed, alongside well grounded mathematical models of resistance selection. These will inform fluke control practices that are more sustainable in the face of anthelmintic resistance.

Tools for complementary control have been investigated to a much lesser extent for *Fasciola* than for nematodes, and research is needed to evaluate their effectiveness and their place in integrated fluke management: including breeding for resistance, nutraceuticals, vaccines, grazing management, and biological control including fungi but also natural predators of snails such as flies, predatory snail species, and birds.

**4) Implement socioeconomic studies to quantify the effects of control methods leading to their optimal use under different scales, geographies and production types aiming to ensure the sustainability of farmers and fluke control business models.**

Cost-benefit analyses are urgently needed to assess the cost-effectiveness against danger of selection for drug resistance, i.e. to achieve a balance of treatments/management options and thus to enable stakeholders to make decisions on the choice of control programme. This includes the economic impact of different levels of infection on animal performance, the cost of an intervention and the benefit gained for individual farms and at national and global levels.

Economic modeling, including partial budget analyses and national economic welfare models, is needed. Grazing management, already widely used to manage *Fasciola*, could be made more precise with the aid of refined epidemiological understanding, and with greater flexibility in regulatory constraints on farm management. For example, policies on wetland environmental management, flood alleviation, and farmer incentives (including single farm payments under the Common Agricultural Policy) are currently poorly aligned and can seriously impede attempts to decrease chemcial use through more creative land management. Research should therefore include the policy context of farm management and be used to inform this policy.

**Summary of the key priority research needs to control Helminth infections of ruminants.**

The control of helminths relies heavily on routine use of chemotherapeutics, but this approach is unsustainable as resistance to anthel­mintic drugs is widespread and increasing. At the same time, infection patterns are being altered by changes in climate, land-use and farming practices. Future farms will need to adopt more efficient, robust and sustainable control methods, integrating ongoing scientific advances.

Here, we present the research priorities of helminth control in farmed ruminants, bringing to bear the research needed in: (1) diagnostic tools, (2) innovative control approaches based on vaccines, (3) Improved therapeutic response against helminth parasites in ruminants and (4) rational integration of future control practices.

1. *Diagnostic tools*

A cross-cutting priority for diagnostic tools is the development of pen side tests and associated decision support tools including (1) the development of more scalable, reliable, less labor-intensive systems for microscopy-based parasite detection including methods of artificial intelligence for automated sample processing and image analysis to generate automated detection and enumeration of parasitic elements and (2) improving reference genomes of major parasite species of importance, applying population and functional genomics approaches to identify and validate resistance mutations as diagnostic markers and developing appropriate molecular diagnostic platforms to allow flexible and affordable molecular based diagnostic tests.

1. *Vaccines*

A cross-cutting priority for vaccines is the development of a polyvalent vaccine that gives long-lasting protection against the predominant nematode species infecting livestock. Both for nematodes and trematodes studies of host transcriptomic responses to infection and identification of protective immune responses (from antigen recognition up to effector responses), including why some animals respond well and others do not, could inform us on strategies for antigen delivery and adjuvants. Finally, based on the antigen's conformation and secondary modifications (e.g. glycosylation), modifiable expression systems will be needed.

1. *Therapeutics*

A cross-cutting priority for therapeutics is the search for approaches to achieve improved therapeutic response for existing anthelmintics in livestock animals in situations where their use is still valid (i.e. some drug susceptible cattle nematodes). There is an urgent need for the identification of novel active pharmaceutical and/or phytochemical ingredients (API) with alternative mode of action and/or expanded therapeutic response against helminth parasites resistant to other available anthelmintic drugs. The elaboration of a target product profile (TPP) to guide the development a novel API with anthelmintic activity is a main initial challenge to be achieved.

Genomic-assisted drug discovery and/or other screening-based technologies to come up with some novel molecules active against multi-resistant helminth parasites

1. *Rational integration*

Validation of pen-side field diagnostic tools to measure levels of infection (egg counts) either for field drug resistance tests, efficacy tests or the identification of individual animals needing treatment. There is a need to build harmonization guidelines or best practice advice to test the different alternative helminth control methods. The latter could help researchers of different laboratories (Governments or Universities) around the world who want to test the different alternative methods, for example, nutraceutical materials or copper needles. The availability of such guidelines/best practice advise could also help publication of results that followed those methodologies. Also needed are standardise methods to quantify effects of alternative control methods; optimisation of their use to maximise production / economic impacts; integration of multiple methods in different environments.

Finally, the combination of worm resistant animals, correct nutritional manipulation and vaccines might render anthelmintic treatments unnecessary. Funding should be targeted for different laboratories willing to work on different breeds of sheep, goats, cattle and horses and should include the exploration of phenotypic results with genotyping, transcriptomic and proteomics.

