Creating a European consortium to study GnRH deficiency (COST Action BM1105)

www.hhnetwork.eu

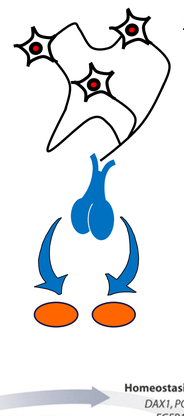
Background

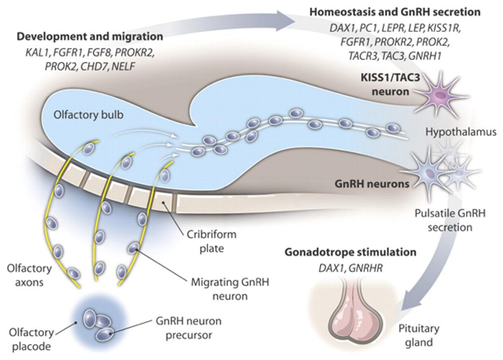
- Reproductive capacity, and thus species survival, depends on a complex organ network involving the hypothalamus, pituitary, gonads, as well as internal and external genitalia.

- This system is centrally controlled by neuroendocrine mechanisms integrated at the hypothalamic level via pulsatile secretion of gonadotropin releasing hormone (GnRH).

- Though all mammalian species depend upon this common pathway to initiate reproduction, relatively little is known about the molecular mechanisms regulating GnRH neuron network.

- Important insights into GnRH biology have come from genetic studies of human mutations resulting in the abnormal development and/or function of GnRH neurons.





Sykiotis et. al., Science Transl Med 2010

The Human Disorder:

- GnRH deficiency ranges from constitutional delay of puberty, to partial puberty, to congenital GnRH deficiency (i.e. normosmic hypogonadotropic hypogonadism or Kallmann syndrome) which presents as a complete absence of pubertal development and infertility.

- While more than a dozen disease genes have been identified, approximately two thirds of patients are without a known genetic cause – indicating that multiple additional regulatory genes and mechanisms remain undiscovered.

The Opportunity:

The rich genetic & phenotypic heterogeneity of this condition represents a unique investigative opportunity to:

- Identify the genes controlling human reproduction
- Explore GnRH biology
- Develop Create novel diagnostic tools & targeted therapies for infertility & reproductive medicine.

Therefore, to fully elucidate the neuroendocrine control of reproduction in health and disease, and to define novel targeted treatments, collaboration on a higher order of magnitude is necessary

Objective & Methods

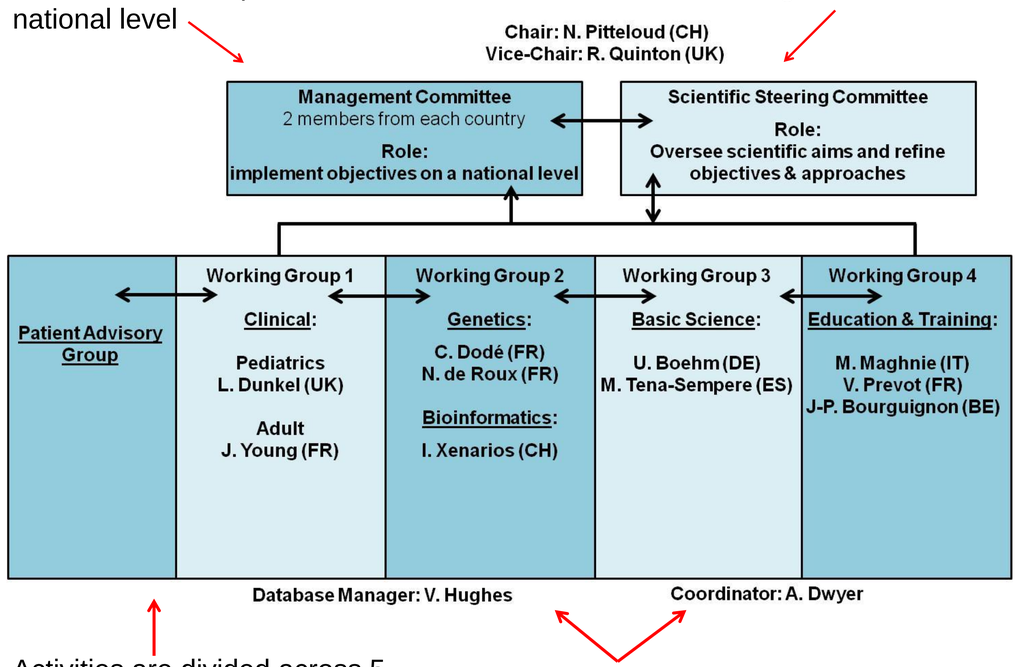
1. Objectives:

Identify genes & mechanisms regulating the neuroendocrine control of human reproduction → Inform/validate human studies using corresponding animal & cellular models → Translate scientific findings into improved patient care, including genetic counseling & patient advocacy.

2. Structure:

Each nation designates 2 members to coordinate & implement at the national level

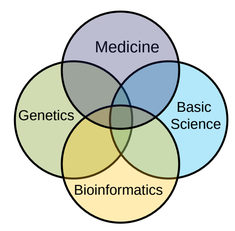
Leaders in the field provide guidance to the Action



Activities are divided across 5 interacting & complementary Working Groups.

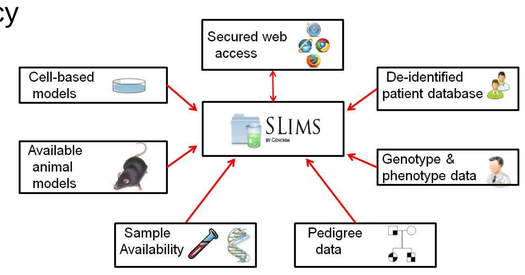
Infrastructure support: website development, customized database, short-term scientific exchanges, & overall project management

3. Major Goals:



- Establish a network of European and near-neighbor experts from a variety of complementary domains to foster research in the field of GnRH biology.

- Create a secured web-based platform for collaboration including a de-identified patient registry for GnRH deficiency that harmonizes existing datasets across Europe and lists available cell-based and animal models.



- Recruit and train young investigators into the field of human reproduction.

- Provide patient education, advocacy & support

4. Deliverables:

WG 1: Clinical

Establish a patient registry and curated web-accessible genotype-phenotype database, publish clinical guidelines, post a listing of specialized referral centers, partner with patients & support groups to develop patient-oriented materials.

WG 2: Genetics & Bioinformatics

Establish genetic counseling guidelines (with WG 1), elucidate the genotype-phenotype correlations (with WG 1), provide expertise for new genetic technologies (i.e. exome sequencing), and explore gene-environment interactions related to GnRH biology/puberty.

WG 3: Basic Science

Characterize the roles of novel disease genes, use expression studies/cellular studies/*in silico* analyses to help prioritize candidate genes identified through next generation sequencing (with WG 2), generate plausible candidate genes from animal models.

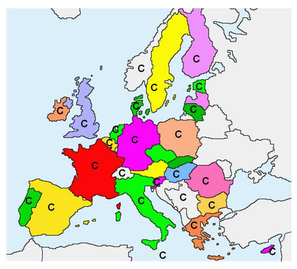
WG 4: Training & Education

Organize & coordinate the summer school program, facilitate Short Term Scientific Missions for investigators (i.e. laboratory exchanges), and coordinate the annual meeting.

Results/Status

1. The Network:

To date, participants from 25 different nations spanning a variety of disciplines have joined to create a geographically and scientifically diverse network for collaboration



2. The Website: www.gnrhnetwork.eu

3. Collaborations: 4 Short-Term Scientific Missions between groups have been sponsored and joint, international proposals for funding have been submitted

4. Joining the Network:

Participants can join the network by contacting the Chair or National Representative - for more info see www.cost.eu/domains_actions/bmbs/Actions/BM1105

Conclusions

- Such a European collaboration will promote scientific synergies across complementary domains and open new avenues for funding opportunities
- The deliverables from this consortium will impact various groups including clinicians, researcher, clinicians, genetic counselors, patients/families, advocacy groups, and European pharmaceutical and biotechnology firms.
- Patient-centered educational and advocacy materials for will be made available in multiple languages reaching previously isolated patients
- For more information see: www.gnrhnetwork.eu, http://www.cost.eu/domains_actions/bmbs/Actions/BM1105, or contact andrew.dwyer@chuv.ch