

Young @ Heart: Call for proposals 'Crazy Idea' Grant

Deadline: Monday 28 August 2017 12:00h pm

On behalf of the Young @ Heart community

Introduction:

The transition from a PhD student into an independent scientist is an essential part of scientific maturation. PhD students start their scientific career by studying a hypothesis conceived by their supervisors, yet often develop their own unique ideas over time. In fact, talented PhD students and early career post-doctoral (post-doc) scientist tend to generate ideas that may revolutionize their research fields, but often lack the resources or support required to explore them. To unleash the potential of early career scientists, several funding bodies have developed talent development programs including the VENI-VIDI-VICI program of NWO and the Dekker program of the Dutch Heart Foundation (DHF). While these talent development programs may aid in the selection of accomplished scientists, they may not support the most revolutionary ideas for several reasons.

First, grading structures of contemporary talent development grants are disproportionately focused on the amount and quality of pilot data, the level of embedding in an existing infrastructure and the ability to complete the proposed research within designated timelines. Such focus on the safety rather than the priority of a proposal, may limit the innovative nature of the proposal.

Second, eligibility criteria for talent development grants invariably limit the time window after PhD graduation in which the candidates can apply. While PhD graduations from Dutch Universities have steadily increased over time, the job opportunities in science have remained unchanged. Many junior post-docs that want to pursue a career in science will be forced to seek employment outside of Dutch knowledge institutions. This may cause them to lose their eligibility before they can secure a position in science.

Third, talent grants are judged by a committee of established scientists from various backgrounds that rely on anonymous reviewers with specific expertise of the topic at hand. Accordingly, the selection procedure is very vulnerable to the availability of suitable reviewers and the quality of their reviews.

Young@Heart (Y@H), the Netherlands Heart Institute (NLHI), the CVON consortia and DHF recognize the urgent need to develop an additional opportunity for novel and inclusive talent

development, focused on the ideas and qualities of individual scientists on top of their established background and support structure. The current “Crazy Idea” grant is the first in a series of grant mechanisms that are being developed by Y@H, the NLHI, the CVON consortia and DHF. The overall aim is to provide early career scientists with the opportunity to test their highly innovative ideas, develop their network and increase their chances to obtain project grants through existing programs. By more broadly involving the expertise of Dutch scientific community and also including the target population of junior scientists in the selection process, we expect that we will be able to overcome the limitations inherent to contemporary grant mechanism and create mobility of skills and talent between groups.

Young @ Heart crazy idea grant

Aim: The Y@H crazy idea grant aims to provide senior PhD students and early career post-docs with the opportunity to test a highly innovative hypothesis.

Type of funding: A maximum amount of 50.000 Euro can be requested that can be used as bench fee, as salary for the candidate or to appoint scientific personnel.

A maximum of two grants will be awarded during an Y@H event; maximum four grants will be awarded each year.

Candidates will be appointed at a Dutch knowledge institution (NLHI included).

Who is eligible?

1. *PhD students* that have performed the equivalent of at least 30 months of full time PhD training. The duration of PhD employment is calculated as the cumulative employment duration equivalent to a full-time appointment. For instance, a PhD student that has been appointed for 0.8 fte. will become eligible after 37 months. Candidates that do not have a date for their thesis defense at the time of submission should submit a letter from their thesis supervisor stating that, if granted, the candidate will be allowed to conduct the research as described in the proposal. The letter should also provide assurance that the allocated funds will be used as specified in the proposal.
2. *Candidates with a PhD-degree* can also apply if they fulfill the following criteria:
 - a. Post-doctoral fellows that have an appointment at a national or international knowledge institution.
 - b. Candidates that have been appointed as an assistant professor (UD) for less than one year. Associate professors and full professors are excluded.

- c. Candidates with a PhD that are currently enrolled in a professional training program (e.g. clinical specialties or pharmaceutical training) and fulfill the criteria as stated in b.
- d. Candidates with a PhD that have been registered as a medical specialist or a pharmacist for less than one year.
- e. Candidates with a PhD that are not currently employed at an national or international knowledge institution and do not fulfill criteria a-d can also apply; provided that they have not previously been appointed as a senior faculty member at a national or international knowledge institution.

Proposal – general

1. The topic of the proposal should be relevant for a CVON consortium. A brief overview of the main aims of all current CVON consortia can be found in **appendix A**. The proposed CVONs may be consulted after submission to determine the relevance of the proposal. Candidates are therefore encouraged to contact a PI from a CVON consortium before submission. Multiple candidates can submit a proposal that is relevant for a specific CVON consortium.
2. A candidate can only submit two Crazy Idea grant proposals and only one proposal per person can be submitted each round.
3. Budget can be spent on the salary for the applicant, on scientific personnel and/or bench fee (salary indication is according to categories of the DHF which can be found on www.cavaris.nl). A maximum of 25 % of the grant can be allocated to support a work visit (travel, housing, bench fee) at a knowledge institution abroad.
4. The application is written in English.
5. Applications are submitted through info@heart-institute.nl

Proposal - content

Cover page

Please add one cover page including applicant's name, affiliation, email, phone number, and brief abstract (max 100 words)

Application

1. A short grant proposal comprising of max. 3 pages A4 (min. font size 11, Arial, single line spacing), including figures and tables; excluding references. The proposal should include the following subheadings:
 - a. Background

- b. Aim
 - c. Methods
 - d. Detailed description of the innovative nature of the proposal
 - e. Description how the topic relates to the aims of an existing CVON consortium and is simultaneously outside of the current scope of the consortium.
 - f. Budget estimate
2. Curriculum vitae.
 3. List of publications.
 4. Letter from the director of a Dutch knowledge institution stating that, if granted, the candidate will be allowed to conduct the research as described in the proposal. The letter should also contain a paragraph describing how the proposal will benefit the scientific development of the talent.
 5. If part of the proposal is carried out at a different knowledge institution than described in 4, written support from the proposed knowledge institution should also be submitted.

Procedure

Submissions and eligibility

1. Deadline for submission (i.e. august 28th 2017, 12:00 PM) will be communicated simultaneously by DHF, NLHI, and Y@H. Submissions will generally close 4 weeks before the next Y@H event.
2. Grants will be checked for eligibility and completeness.
3. Applicant should be present on the next Y@H event on Friday 29 September.

Judging

1. The CVON consortia that are still active on January 1st of the year of the grant call or will become active within that year will be involved in the judging process. The talent coordinators from these CVONs will be randomly allocated to group A or group B. In addition, members of the Y@H board and scientific council that have not submitted a proposal will also be randomly allocated into group A or B. In the first round of that year, group A will judge the initial proposals and the talent coordinators from the CVON consortia of group B will judge the pitches and determine the eventual winners during the Y@H event as described below. For the second round, group B will do the initial judging and the talent coordinators from the CVON consortia in group A will vote during the Y@H event.

2. During the first round, all proposals will be judged by all jury members. Proposals will receive three grades (1-10) from every individual judge for:
 - A. Scientific priority of the proposal (this will be weighed for 60%). The proposal should be highly innovative in nature with a “high risk - high potential” profile.
 - B. Feasibility of the proposal (weighed for 20%)
 - C. Track-record of the candidate (weighed for 20%)
3. The judges will submit their grades to the NLHI as described above
4. We acknowledge that it is more difficult to submit a proposal from outside a CVON consortium than from within an existing network. Furthermore, we aim to promote the mobility of talent and attract talented researchers from different fields. Therefore, in cases of equal ranking, mobility from outside a consortium will be rewarded extra.
5. Each proposal will be ranked based on their median grade.
6. The top 5 applicants will be selected to pitch their idea during a Y@H meeting. Before the formal invitation, the talent coordinators of the proposed CVON consortia will be consulted to verify that the proposed research is relevant for their consortia.
7. All candidates (including those that have not been selected) will receive their median grades for the scientific priority, feasibility or for their track record.
8. The pitch will take 5 minutes and the candidate will answer one question from the judges and one from the audience (the most relevant digital question from the audience will be selected by the moderator).
9. The pitches will be judged by a jury of representatives from CVON consortia and the participants of the Y@H meetings. Each jury member and each participant of the Y@H meeting chose their top 3 candidates, by providing 3 points to the first candidate of preference, 2 to the second, and 1 to the third. The other two candidates receive 0 points. Each candidate has to attend the pitches by themselves. Representation by someone else or via modern media is a reason for disqualification.
10. To obtain voting rights, the participants of the Y@H meeting will need to register through the online voting platform at the beginning of the meeting.

11. All 5 pitches will be ranked according to the mean composite score of the CVON jury members (making 60% of the final score – see point 3 of the Procedure) and the mean score of the participants of the Y@H meeting (making 40% of the final score). The two proposals with the highest composite score will receive a *Crazy Idea* grant.

Initiation: The project should be initiated within 6 months after allocation.

During execution: The awardee will find a mentor from the Y@H mentor database and will have at least two mentor discussions during the project period.

Reporting: After the project has been completed, awardees will write a final report, including full justification of the budget. The candidate will be invited to present the outcomes of the project at a Y@H event.

Contact and information:

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CVON2011-11

ARENA

Approaching Heart Failure by translational research of RNA mechanisms

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Summary

Heart failure (HF) is a syndrome that mainly affects elderly patients. Current therapies have provided benefit, but conceptually novel treatments, particularly for diastolic dysfunction, are conspicuously lacking. A large part of the hearts' response to overload has not been fully understood. We know that the cardiac genome accumulates responses to continuous overload, but studies have traditionally focused on the protein coding part of the genome. This focus on protein based mechanisms fails to appreciate a large part of the cardiac genomic response, where noncoding RNAs (ncRNAs) play an important regulatory role and may provide better understanding of the different subtypes and stages of HF progression. Recent advances in the field of microRNAs provide novel possibilities that are on the brink of clinical application. The surprising stability of circulating microRNAs has opened the possibility to develop next generation biomarkers. Inhibition of selected microRNAs is powerful and holds great promise to become the next generation therapeutics. Since microRNAs and their targets are genomically encoded, genetic principles apply and create 'microRNA genetics' as a source of individual variation. ARENA aims to mine the wealth of these ncRNA mechanisms to enable the development of next generation RNA based diagnostics and therapeutics. Each work package is based on recently generated data within the consortium to provide the necessary proof of concept. We expect ARENA to a) address the clinical added value of newly identified RNA based mechanisms and b) use the unique models combined in ARENA to mine the wealth of ncRNAs in HF.

CVON2011-12

HUSTCARE

Human **S**tem cells for **C**ardiac **R**epair

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Summary

Stem cell therapy for the heart is safe but has been most successful in improving cardiac function in clinical trials where preclinical research demonstrated activation of endogenous repair in the host heart tissue. Cardiac repair includes neovascularization and inflammation, endogenous cardiomyocyte and progenitor cell proliferation and differentiation. We hypothesize that deeper understanding of these mechanisms in animal models by directly comparing the effects of different stem cell types from different patients will lead to (i) identification of the best cell types and co-factors for therapy, and (ii) parameters that predict which patients are most likely to benefit from autologous versus heterologous cell transplantation. Candidate cells for comparison are mesenchymal stem cells (MSC) and cardiac stem cells (CSC). Candidate co-factors and mediators of paracrine mechanisms will include growth factors, delivered through slow release beads, and miRNAs that control differentiation. These factors have already been implicated as mediating endogenous cardiac repair; the goal here will be in examining their value in enhancing the effect of cell transplantation. We will not only use novel transgenic mouse models for these mechanistic and optimization studies but will also extend the investigation to pigs that have undergone myocardial infarction. Novel will be (i) investigation of the role of inflammation and the immune response on cardiac recovery following cell transplantation (ii) quantitative analysis of endogenous cardiac progenitor cell recruitment/cardiomyocyte proliferation (iii) determining the impact of CVD predisposition and gender in diagnostic bioassays to distinguish responding and non-responding patients retrospectively (iv) applying this information to ongoing and future trials.

CVON2011-19

GENIUS

Generating the best evidence-based pharmaceutical targets for atherosclerosis

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Summary

Statins reduce the burden of cardiovascular disease (CVD) by 25%, underscoring an urgent need for pharmaceutical targets suitable for new drug development. Over the last decade, numerous targets have emerged but have not led to successful treatment of patients. The 92% failure rate of novel drugs is primarily due to a lack of preclinical phenotyping and metabolic network analysis, which in turn is related to a poor translation of scientific insight to clinical application. GENIUS has the potential and power to bridge this gap by realizing state-of-the-art translational science with a unique team of top basic and clinical scientists. We will take a different route to discovering new and better targets for pharmaceutical intervention by placing the patient with CVD at the centre. This will be realized through advanced genetics, metabolomics, proteomics and systems biology approaches in large, unique cohorts of patients. GENIUS will importantly subject potential targets from top level basic research to human validation steps: we will study the relation of these targets with CVD in prospective and patient cohorts and through research in human biobanks. Targets that pass these tests will be prioritized and studied in mechanistic studies in mice in which we will aim to further unravel the molecular pathology of atherosclerosis. We will also study the feasibility and efficacy of pharmaceutical intervention. To better understand the etiology of atherosclerosis and to find new targets, GENIUS will focus on the interactions between dyslipidemia and immune networks, since we hypothesize these interactions dictate the process of atherogenesis.

CVON2012-01**1-Valve****One Valve for life*****Research Leaders Consortium***

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Summary

Valve replacement with mechanical or bioprosthetic prostheses is the most common intervention for valvular disease, with almost 300.000 annual replacements worldwide. There are more and more patients with grown up congenital heart disease (GUCH) who have survived into adulthood thanks to surgical innovations and will require one or more heart valve replacements later in life. Although existing valve prostheses generally have resulted in enhanced survival and quality of life, prosthesis associated problems affect 30-35% of the patients within 10 years post operatively. In particular young recipients of current heart valve replacements have significantly reduced life expectancy (up to 50%) compared to age matched healthy individuals, and experience a high probability of serious valve-related morbidity throughout life. In patients younger than 18 years freedom from reoperation is only 58-68% at 15 years.

Recently, in situ tissue engineering using endogenous cells recruited from the bloodstream has emerged as a promising alternative to create living heart valves having the potential to grow, repair and last a life-time: one valve for life. Compared to classical tissue engineered heart valves, this new technology has off-the-shelf availability at substantially reduced cost. The current proposal aims to deepen the mechanistic understanding of the in situ tissue engineering of heart valves, and to translate this exciting technology to enable first-in-man clinical application. To this end, we combine basic research on in-vitro and in-vivo models of in-situ heart valve engineering with long-term preclinical studies and early Health Technology Assessment.

CVON2012-03**In-control****The role of the gut microbiota and chronic inflammation as drivers of cardiovascular disease*****Research Leaders Consortium***

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Summary

There is overwhelming evidence that chronic inflammation plays a driving role in both metabolic and cardiovascular diseases (CVD). Whereas the detrimental roles of chronic, low-grade inflammation in adipose tissue and fatty liver have been studied intensively, we still need to elucidate the primary causes of proinflammatory changes in patients at increased risk of CVD. We hypothesize that the activation of chronic inflammation is initiated and driven by a disturbed interaction between the intestine, liver and adipose tissue. Insight into the mechanisms leading from pro-inflammatory processes in the intestine to adipose tissue and liver inflammation is now emerging and recent data point at a pivotal role for the inflammasome and autophagy in triggering and modulating the subsequent activation of the chronic inflammatory responses. However, there is still insufficient insight into inflammatory mechanisms to translate this knowledge into potential clinical therapeutic strategies.

We aim to study well-characterized patient cohorts with obesity and CVD traits. We will also take advantage of extensive cohort studies for an integrative genomic approach to determine the causes of chronic inflammation and the role of genetic factors, aging and gut microbiota in this process. Studies in mouse models will improve our mechanistic understanding and help evaluate potential therapeutic interventions. Our project will address the direct link between the primary inflammatory response, over-nutrition and cardiovascular diseases now prevalent in humans. The results should lead to novel nutritional products, biomarkers for diagnosis and monitoring the effects of treatment, and anti-inflammatory therapies for the prevention of CVD.

CVON2012-06

HBC

The heart brain connection: the missing link in the pathophysiology of vascular cognitive impairment

Research Leaders Consortium

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Summary

While both cardiac dysfunction and progressive loss of cognitive functioning are prominent features of an aging population, surprisingly few studies have addressed the link between the function of the heart and brain. This is probably due to the monodisciplinary approach to these problems by cardiologists, neurologists and geriatricians. Recent data indicate that autoregulation of cerebral flow cannot protect the brain from hypoperfusion when cardiac output is reduced or atherosclerosis is prominent. This suggests a close link between cardiac function and large vessel atherosclerosis on the one hand and brain perfusion and cognitive functioning on the other. In the current research proposal we will test the hypothesis that the hemodynamic status of both the heart and the brain is an important and potentially reversible, but underestimated cause of vascular cognitive impairment (VCI) that may offer promising opportunities for treatment. In a truly multidisciplinary approach we will address the following questions. 1) To what extent do hemodynamic changes contribute to VCI? 2) What are the mechanisms involved? 3) Does improvement of the hemodynamic status lead to improvement of cognitive dysfunction? To this end we will perform new clinical studies in elderly patients with either clinically manifest VCI, carotid occlusive disease or cardiac dysfunction and evaluate their cardiac and large vascular function, atherosclerotic load and cerebral perfusion with the same MRI based protocol and thoroughly test their cognitive dysfunction. We will also analyse epidemiological data from the Rotterdam study and use animal studies to dissect the mechanisms involved and to reveal novel leads for interventions.

CVON2012- 08

Phaedra

Pulmonary Hypertension and associated Right Heart Failure (Phaedra): breaking the vicious circle

Research Leaders Consortium

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Summary

A high pressure in the pulmonary circulation (pulmonary hypertension, PH) complicates several highly prevalent chronic diseases, including left heart failure and chronic thrombo-embolic disease. Pulmonary arterial hypertension (PAH) is a fatally progressive form of PH with characteristic changes in small lung arteries, affecting 1/50.000 humans. Regardless of primary cause, PH almost invariably leads to right heart failure and death. While vasoconstriction and vascular remodelling play some role in all forms of PH, the underlying mechanisms are incompletely understood. Mutations in the type II receptor for bone morphogenetic protein (BMP) are responsible for 80% of heritable PAH cases, yet deregulation of BMP signalling also occurs in non-hereditary forms of PAH. BMP is frequently antagonized by transforming growth factor- β (TGF- β). We hypothesize that an imbalance in TGF- β and BMP signalling and a vicious circle of alterations in pulmonary blood flow velocity and pressure are at the basis of vascular remodelling in all types of PH. Our aim is to break the vicious circle in a multidisciplinary approach in which patient and preclinical material is used to characterize altered TGF- β /BMP signalling and pulmonary vascular remodelling. Specific drugs will be identified to normalize the TGF- β /BMP imbalance and tested in preclinical models, thereby working towards clinical application. We will identify key factors which increase the vulnerability to develop PH and sustain the vicious circle of alterations in hemodynamics, vascular remodelling and right heart dysfunction. Our collaboration will define new strategies to assess, prevent and reverse pulmonary vascular remodelling and improve right heart function.

CVON2012-10

PREDICT

Predict Sudden Cardiac Death

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Summary

Sudden cardiac death (SCD) causes 50% of cardiovascular deaths in The Netherlands, yet is the first sign of heart disease in 50%. Breakthroughs in development of individualized preventive strategies are hindered by insufficient knowledge of its molecular determinants. Ventricular fibrillation (VF) is the most common underlying arrhythmia. In the last 15 years, we have focused on Mendelian rhythm disorders associated with SCD, obtaining valuable mechanistic insights. In PREDICT, while we still address current important issues relating to these disorders we also apply fundamentally new approaches to study the genetic basis of SCD in large well characterized cohorts of SCD patients from the general community. In the latter we focus specifically on VF in the setting of a first acute myocardial infarction, a highly prevalent and specific arrhythmia phenotype.

PREDICT has three major components:

A. A gene-discovery component which aims to uncover novel genes involved in (i) VF/SCD in the community and (ii) VF/SCD in the Mendelian rhythm disorders. This is essential to uncover yet-unknown players/pathways in cardiac electrical function and arrhythmia and provide tools for research into mechanistic insight, novel drug targets, and risk stratification.

B. A mechanistic analysis component which will study (i) genetic loci already known to be involved in cardiac electrical function /arrhythmia but for which the exact gene and mechanism remains unknown, as well as (ii) novel genes identified in PREDICT.

C. A clinical component which besides testing specific topical hypotheses in the field will also provide a structure to test and validate clinical hypotheses generated by A and B.

CVON2014- 02**Energise****Targeting energy metabolism to comBAT cardiovascular disease*****Research Leaders Consortium***

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Summary

Obesity is recognised as a major determinant of cardiovascular disease. However, major knowledge gaps exist in understanding the pathologic mechanisms, which hampers targeted prevention. Besides overall obesity, the distribution of excessive fat, specifically fat accumulation in and around organs such as liver, heart and skeletal muscle, is an emerging risk factor for cardiometabolic disease. Whereas prevention in the last decades has focused on reducing energy intake, long-term maintenance of healthy weight is difficult. We postulate that increasing energy expenditure can offset many of the negative health consequences of obesity. Besides exercise, we have discovered activation of brown adipose tissue (BAT) as a novel target in humans to increase energy metabolism, which in turn may translate into cardioprotective properties. In both muscle and BAT, mitochondria and peroxisomes play a pivotal role in the regulation of energy metabolism, and improving their function is a key-target for prevention of obesity-related cardiometabolic disorders. The aim of this project is to elucidate the role of enhancing energy metabolism in the prevention of cardiovascular/atherothrombotic disease. We will combine mechanistic studies in mice and cell systems with genomics, lipidomics, and metabolomics-based approaches in a large well-characterized and unique human obese cohort. Translational observational and intervention studies in humans will be complemented by pathway analyses and mathematical modelling approaches to identify targets and biomarkers for disease. We anticipate that this will lead to novel behavioural and pharmacological (preventive) therapies and biomarkers for prevention of obesity induced diabetes and cardiovascular disease.

CVON2014-09

Race V

Reappraisal of Atrial Fibrillation: Interaction between hyperCoagulability, Electrical remodeling, and Vascular Destabilisation in the Progression of AF

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Summary

Atrial fibrillation (AF) is not benign and manifests both as electrical and hypercoagulable disease. AF progression alludes to the tendency of AF to become persistent (electrical progression) but also to enhanced stroke risk (vascular progression). The electrical, hypercoagulable and vascular aspects of AF have traditionally been investigated by different research groups with little attention for potential cross-links. Yet, hypercoagulation, vascular remodelling and tissue fibrosis tightly interact to cause thromboembolic events but also to promote AF itself. Furthermore, new mechanisms of atrial remodeling are currently emerging like fatty infiltration or amyloidosis. All these mechanisms interact with the individual genetic background which has been demonstrated to significantly alter the risk for AF. We therefore propose to investigate AF progression in a network of scientists with expertise in electrophysiology, blood coagulation, vascular physiology and genetics. In 4 basic research packages we study how AF affects blood coagulation and vascular function and how – vice versa – hypercoagulation and vascular alterations enhance atrial structural remodelling and AF. We also study how common gene variants affect gene expression in the atria and how they modify the effect of these mechanisms on the progression of AF. Translation of the new knowledge to patients will be implemented in two clinical work packages. In a registry including thoroughly characterized patients with documented new onset subclinical AF or paroxysmal AF determinants of AF progression will be assessed including blood biomarkers of hypercoagulation, inflammation, and fibrosis. In a sentinel randomized trial we aim to find evidence that amelioration of hypercoagulation with a Xa blocker reduces AF progression. Finally, we will develop a multimodal prediction model for AF progression based on clinical data, biomarkers, miRNA and common gene variants.

CVON2014- 11

Reconnect

Renal connection to microvascular disease and heart failure with preserved ejection fraction

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Summary

Heart failure (HF) is a major health care problem associated with high morbidity and mortality. Although advances have been made in treatment of HF patients with reduced ejection fraction (HFrEF), this is not true for HF patients with preserved EF (HFpEF). Recently, our consortium demonstrated that albuminuria and impaired kidney function are strong risk factors and predictors for mortality in HFpEF. However, the mechanisms by which a limited decline in kidney function and its systemic and metabolic consequences aggravate HFpEF are poorly understood. Recent insights indicate a central role for the microvasculature in HFpEF aetiology, and a causal relation between impaired kidney function and microvascular dysfunction. This consortium will test the hypothesis that renal impairment and its systemic consequences adversely impact the coronary microvasculature, modifying pathophysiology, course and progression of HFpEF. We will assess the renal drivers of HFpEF onset and progression, allowing identification of early prognostic factors and targets for (personalized) intervention. We will take advantage of several available patient cohorts, combined with mechanistic in vitro and in vivo studies to 1) evaluate (pre-defined and novel) systemic circulating factors in CKD-induced HFpEF, 2) elucidate the CKD-induced epigenetic regulatory mechanisms that contribute to microvascular dysfunction and HFpEF, 3) study the mechanism of CKD-induced HFpEF, and test promising therapeutic targets, in small and large animal models, and 4) explore and validate novel prognostic serum profiles for HFpEF. The results of this project will enhance our mechanistic insight in the renal drivers of HFpEF development and progression, allowing more customized and personalized therapeutic solutions for HFpEF patients.

CVON2014-18

CONCOR-GENES

Genetics of congenital heart defects and its implications for adult heart disease

Research Leaders Consortium

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Summary

Cardiac heart malformations, affecting 7 per 1000 live births, constitute a major fraction of clinically significant birth defects and represent an important component of pediatric and adult cardiovascular disease. Although there have been tremendous advances in diagnosis and treatment of congenital heart disease (CHD), our knowledge of causes of CHD is very limited. Recent clinical and basic research has shown the importance of genetic factors in causation of CHD. The novel high-throughput sequencing technologies that have recently become available (namely next-generation sequencing) are now expected to provide an important impetus for CHD gene discovery, even in cases with sporadic (non-familial) presentation. We here hypothesize that knowledge of the exact genetic cause in individual patients is important since it could provide prognostic information about the clinical course of the disease throughout life, which is known to vary among patients with CHD. Furthermore, it enables reproductive counseling of the large population of adult patients with CHD. In this study we shall use next-generation sequencing to uncover genetic variations causing CHD, focusing on patients with conotruncal malformations from the CONCOR national registry. We shall collect clinical data related to late complications and investigate whether specific relations exist between the type of CHD gene involved and the development of specific late complications. We shall validate newly-identified genes by means of mechanistic embryological studies in model organisms such as zebrafish and mouse. This study shall set the first and very exciting step to uncover on a large-scale novel CHD genes in the national CONCOR registry.

CVON2014- 27

Remain

Hydrogel-based delivery of microRNA therapeutics to enhance cardiac regeneration

Research Leaders Consortium

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Summary

With the growing incidence of cardiovascular morbidity and mortality, regenerative therapies are becoming increasingly important for treating ischemic heart disease. Over the last decade it has become clear that microRNAs (miRNAs) are important players during heart disease and present an exciting new class of drug targets for the treatment of patients. Based on lessons learned from siRNA very potent chemistries exist to therapeutically inhibit or increase miRNAs, however systemic delivery of these drugs reduces cardiac exposure and can introduce unwanted side-effects in tissues besides the heart. Efforts focused on enhancing cardiac delivery of these novel therapeutic modalities, might have far reaching indications for their therapeutic applicability and might further increase our excitement around using microRNA modulators as new therapies for heart disease.

Recently, the groups of Dankers (TU/e) and Chamuleau (UMCU) showed that a pH-responsive supramolecular hydrogel based on four-fold hydrogen bonding ureido-pyrimidinone (UPy) units and poly(ethylene glycol) (PEG), can be used to effectively deliver drugs to the infarcted myocardium via a minimally invasive catheter delivery. Sustained release of bioactive growth factors using this UPy-hydrogel led to a significant reduction in scar formation after myocardial infarction in a porcine model. Unpublished data from the group of van Rooij (Hubrecht Institute/UMCU) indicate that inhibition of miR-1 and increased levels of miR-19 has cardioprotective effects during ischemic injury to the heart. In an attempt to enhance the pharmacological activity of these drugs by creating a drug depot, while reducing the risk for unwanted toxicities, we propose that with the combination of microRNA therapeutics (van Rooij), intelligent pH-switchable UPy-hydrogels (Dankers) and catheter delivery technology (Chamuleau) we are able to locally deliver and release microRNAs via minimal invasive application. Furthermore, we propose that by varying the supramolecular structure of the UPy-hydrogelators we can adjust and control the release of the anti-miR-1 and miR-19 mimics. In vitro experiments, and in vivo efficacy studies in both a rodent and porcine model of ischemic injury will allow to study whether hydrogel-based delivery of miRNA therapeutics enhances the efficacy of miRNA therapeutics and whether cardiac delivery of anti-miR-1 and miR-19 mimic improves cardiac regeneration during ischemic injury.

CVON2014-40

Dosis

Determinants of susceptibility in inherited cardiomyopathy: towards novel therapeutics approaches

Research Leaders Consortium

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Summary

Inherited cardiomyopathies (CM) are clinically highly variable and show age-dependent and variable penetrance, i.e. age of onset in patients with the same mutated gene can vary from early age to senescence. But even for a given mutation in one gene, onset and disease severity largely differ implying that additional determinants, including genetic variations, environmental and/or toxic disease triggers, and an age-related decline in protective mechanisms (protein quality control (PQC) system) impede on disease susceptibility. The PQC system prevents derailment by sequestering the mutant protein and subsequent toxic protein accumulation in the cardiomyocyte. Moreover, derailment is attenuated by the stimulation of protein degradation pathways, including autophagy. Thus, a healthy PQC system keeps mutant expression below the toxic dose and prevents the pathogenicity and onset of cardiomyopathy. In addition to secondary disease factors, location of a specific mutation in a gene might determine disease susceptibility. We hypothesize that severity of functional and structural impairments and capability of the PQC system to counteract the mutant protein depend on specific mutation-induced changes in protein structure.

We aim to I) identify additional genetic and environmental mechanisms responsible for increased expression and toxicity of mutant protein during ageing, to uncover the role of derailed PQC system in CM and test whether boosting of PQC counteracts disease onset and severity. In addition we aim to II) establish whether mutation location determines its expression by recognition by PQC, its incorporation in the sarcomeres and its functional consequences and finally test whether therapies to normalize the PQC system and increase contractile strength can prevent and/or delay mutation-induced defects of the heart muscle.

CVON 2015-01**Contrast
Collaboration for New Treatments of Acute Stroke*****Research Leaders Consortium***

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Summary

In MR CLEAN we have recently shown that intra-arterial therapy (IAT) with the use of a retrievable stent improves outcome in selected patients with acute ischemic stroke (AIS) and a proximal intracranial artery occlusion. This benefit has been confirmed in four other trials. Still, major challenges in the treatment of acute stroke remain. First, still two thirds of the patients treated with IAT in MR CLEAN were dead or dependent at 3 months. Secondly, only 10% of patients with AIS are eligible for IAT to date. And thirdly, about 15% of all strokes are intracerebral hemorrhages (ICH), for which treatment options are very limited.

CONTRAST aims 1. To achieve faster optimal stroke treatment for more patients; 2. To develop and test new treatments for a broad population of patients with ischemic stroke or ICH; and 3. To broaden the indication for IAT and increase its benefits.

These aims will be reached through joined efforts of basic and clinical scientists. We will perform five large acute stroke trials to test novel treatment strategies, including 1. pre-hospital augmentation of collateral blood flow and blood pressure reduction; 2. antithrombotics to prevent microvascular occlusion after IAT; 3. immediate IAT without preceding thrombolysis; 4. IAT in the 6 to 12 hour time window; and 5. microsurgical hematoma evacuation and dexamethasone in patients with ICH. We will 1. aim to identify patients who will benefit from these interventions through advanced imaging; and 2. we will develop novel stroke treatments with animal models, in combination with data from our clinical biobank, which stores blood, plasma and thrombi; and 3. apply discrete event modelling (DES) with data from the trials, to optimize stroke care.