GRANT AGREEMENT

This Grant Agreement ("**Agreement**") is entered into as of 18th of September 2018 ("**Effective Date**") by and between Novartis Healthcare A/S, Reg. No. 20575786, a company incorporated under the laws of Denmark, located at Edvard Thomsens Vej 14, DK-2300 Copenhagen S, Denmark ("**Novartis**") and Aarhus Universitetshospital, Medicinsk hepato- og gastroenterologisk afd. V, a hospital department incorporated under the laws of Denmark, located at Nørrebrogade 44, 8000 Aarhus, ("**Grant Recipient**"). Novartis and Grant Recipient may hereinafter be referred to individually as a "**Party**" and collectively as the "**Parties**".

WHEREAS, Grant Recipient has specifically requested Novartis' financial contribution in order to support the Grant Activity (as defined in Exhibit A), through a Grant Request Letter, which is attached hereto as Exhibit B;

WHEREAS, in accordance with the Grant Request Letter mentioned above, Novartis wishes to support the Grant Activity with the Grant Amount (as defined in Exhibit A); and

WHEREAS, Grant Recipient accepts the Grant Amount subject to the terms and conditions of this Agreement.

NOW THEREFORE, in consideration of the premises and the mutual covenants herein contained, it is mutually agreed as follows:

1. GRANT BY NOVARTIS

1.1 **Grant**. Novartis will provide the Grant Amount as set forth in Exhibit A solely to support Grant Recipient in performing the Grant Activity as set forth in Exhibit A.

1.2 **Statement of Purpose**. The Grant Activity is for scientific and/or educational purposes only and will not promote Novartis' products, directly or indirectly. The Grant Amount is not being given in exchange for any explicit or implicit agreement to purchase, prescribe, recommend, influence or provide favorable formulary status for any of Novartis' products. The Grant Amount is based upon a budget provided to Novartis by Grant Recipient reflecting a good faith estimate of the actual cost of the Grant Activity. The Grant Amount has not been determined in a manner that takes into account the volume or value of referrals or business, if any, generated between Novartis and Grant Recipient or any of their respective officers, directors, employees, agents, affiliates, parents or subsidiaries.

1.3 **Novartis Responsibility**. Grant Recipient agrees that Novartis' responsibility is solely to provide the Grant Amount. Novartis will not be liable to Grant Recipient or to any other person for the Grant Activity or the use of the Grant Amount (including any claims or losses related thereto). Novartis may terminate this Agreement and require Grant Recipient to return the Grant Amount and take other corrective action if Grant Recipient breaches this Agreement.

2. OBLIGATIONS OF GRANT RECIPIENT

2.1 **Use of Grant Amount**.

(a) Grant Recipient shall use the Grant Amount solely for the Grant Activity and shall not use the Grant Amount for any activity that is inconsistent with, or prohibited by any law, rule or regulation. The Grant Recipient undertakes to independently contact Novartis in the event any part of the

Grant Amount has not been used for the Grant Activity so that such amount can be refunded to Novartis without undue delay.

(b) Grant Recipient will comply with (and shall be solely responsible for any failure to comply with) all relevant laws, rules and regulations (including any code of practice or other guidelines generally followed by pharmaceutical companies in the relevant country) in connection with the Grant Activity. Grant Recipient warrants that the Grant Activity is compliant with all such requirements.

(c) Grant Recipient is solely responsible for the manner in which the Grant Amount is disbursed, recorded and accounted and for all contractual and other relationships with third parties relating to the Grant Activity and the use of the Grant Amount. Any claims for payment from third parties involved in the Grant Activity are the sole responsibility of Grant Recipient and Novartis will not fund any additional amounts for the Grant Activity.

2.2 **Objectivity & Balance**.

(a) The Grant Activity will be independent, non-promotional and free from commercial influence or bias.

(b) If the Grant Activity involves the discussion of Novartis products, or the comparison of Novartis products with other products, that discussion and/or comparison must be objective, balanced, accurate, not misleading or deceptive and in compliance with all applicable laws, rules and regulations. Where appropriate, the Grant Activity will include a discussion of multiple treatment options, and will not focus on a single product.

(c) Grant Recipient will ensure that any titles or overview information relating to the Grant Activity will fairly and accurately represent the scope of the planned activity.

(d) If required, Grant Recipient is responsible for selection of presenters, moderators and collaborators for the Grant Activity. Novartis will not control the planning, content, speaker selection or execution of any Grant Activity. If Novartis suggests presenters, moderators or collaborators, Grant Recipient will record the role of Novartis in making the suggestion, seek other sources and make a final selection based on balance and independence.

2.3 **Disclosure of Financial Relationships**.

(a) Grant Recipient will: (i) disclose, to all audiences and in all publications relating to the Grant Activity, that Novartis has provided a grant to support the Grant Activity; (ii) acknowledge support from Novartis in brochures, syllabi, and other materials related to the Grant Activity; and (iii) disclose any other relationships Novartis has with any individual speakers, moderators, collaborators or Grant Recipient which a reasonable and ethical person would expect to be disclosed.

(b) Novartis may disclose publicly the financial and non-financial support provided to Grant Recipient, including, without limitation, the Grant Recipient's identity, the Grant Amount and purpose of the support.

2.4 **Ancillary Activities**.

(a) If the Grant Activity occurs as part of an overall activity that includes commercial activities, such activities will neither influence planning nor interfere with the Grant Activity. No commercial

activities will be permitted in the same room as an educational activity, unless (i) this is allowed in the country in which the activity will take place and (ii) only to the extent that such commercial activity does not interfere with the purpose of the Grant Activity.

(b) The scheduling of meals and/or receptions, if any, in connection with any portion of the Grant Activity is at the sole discretion of Grant Recipient. Meals and/or receptions, if any, will be modest and conducive to the Grant Activity, and the amount of time at the meals or receptions will be clearly subordinate to the overall amount of time.

(c) Reconciliation of Expenses. At the conclusion of the Grant Activity, Grant Recipient will provide to Novartis a reconciliation of the actual expenses versus estimated expenses and will issue a refund to Novartis for any portion of the Grant Amount not incurred in the implementation of the Grant Activity. In addition, Grant Recipient will retain appropriate records of the Grant Activity and the use of the Grant Amount and will provide evidences (as further specified in Exhibit A) to Novartis to document that the Grant Amount has been used in accordance with this Agreement.

3. GENERAL

3.1 **Entire Agreement**. This Agreement, together with its Exhibits, sets forth the entire agreement and understanding of the Parties as to the subject matter hereof and supersedes all proposals, oral or written, and all other prior communications between the Parties with respect to such subject matter. In the event of any conflict between a substantive provision of this Agreement and any Exhibit hereto, the substantive provisions of this Agreement shall prevail.

3.2 **Governing Law and Jurisdiction**. This Agreement shall be governed by and construed under the laws of Denmark, without giving effect to the conflicts of laws provision thereof. Any dispute or claim arising out of or in connection with this Agreement which cannot be settled amicably between the Parties, is to be brought before the Maritime and Commercial Court in Copenhagen or, if this court is not competent, before a competent court of law in the Kingdom of Denmark.

3.3 **Counterparts**. This Agreement may be executed in two or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument.

IN WITNESS WHEREOF, the Parties intending to be bound have caused this Agreement to be executed by their duly authorized representatives.

NOVARTIS HEALTHCARE A/S

By: Elisabet Oladottir

Signature: DocuSigned by: Elisabet Oladottir 6460C1B340804AD...

Title: Medical Advisor

Date: 24-Sep-2018 | 11:44:21 AM EDT

Århus Universitetshospital

By: Jens Kelsen

Signature: DocuSigned by: Jens Kelsen B13C383396EB46A...

Title: Overlæge, PhD

Date: 24-Sep-2018 | 1:32:04 PM EDT

By: Erik Heegaard

Signature: DocuSigned by: Erik Heegaard 65E1D5659F45487...

Title: Medical Director Nordics

Date: 24-Sep-2018 | 9:00:06 AM EDT

EXHIBIT A

GRANT AMOUNT & GRANT ACTIVITY

Grant Amount: ***150.000*** DKK

Grant Activity: Funding for a project on circulating tumor DNA in Neuroendocrine tumors. The funding is to be used to pay for laboratory expenses in connection with a stay at the University College/Royal Free Hospital. The laboratory expenses will be covering tumor mutation profiling of the samples collected in the project. The grant can´t be used to pay for any other expenses connected to the stay at University College/Royal Free Hospital.

Evidences must be provided to Novartis upon completion of the Grant Activity:

The grant recipient is required to confirm to Novartis within two months from conducting the activity that the grant has been used for the purpose intended by submitting the final budget of the meeting.

The Grant amount is payable against the corresponding invoice within sixty (60) days of its receipt and at the end of a calendar month.

The invoice shall include all details (including a Purchase Order Number) as specified in the Purchase Order received by Grant Recipient at the following email address: jenskels@rm.dk

EXHIBIT B

GRANT REQUEST LETTER

Aarhus Universitetshospital
Lever-, Mave- & Tarmsygdomme

Palle Juul-Jensens Boulevard 99,
Indgang C
8200 Aarhus N
Tlf. 78453800
www.auh.dk

Elisabet Oladottir

Medical Advisor, Oncology
Novartis Healthcare A/S
Edvard Thomsensvej 14, 3. sal
2300 København S
Denmark

midt regionmidtjylland

Dato 31.0.18

Ansøgning om støtte til analyseudgifter i forbindelse med forskningsophold ved Royal Free Hospital i London

Vi tillader os hermed at ansøge om støtte til læge, PhD-studerende Stine Karlsens studieophold ved University College London og Royal Free Hospital, London i januar og februar 2019.
Forskningsenheden University College London er sammen med den kliniske afdeling på Royal Free Hospital et af de førende centre i verden til behandling af neuroendokrine tumorer (NET). De har et stort patientflow og en aktiv forskningsenhed.
Royal Free Hospital har gennem en årrække arbejdet med genetiske analyser af NET under ledelse af Christina Thirlwell og har publiceret adskillige artikler om genetiske og epigenetiske forandringer i NET. Samtidig har de stor kompetence indenfor molekylærbiologiske metoder og Christina Thirlwell har givet tilsagn til Stine Karlsens ophold
Målet med opholdet på Universtity College/Royal Free Hospital er tredelt. Dels at undersøge prøver, der er indsamlet under Stine Karlsens PhD-projekt i Danmark for cirkulerende tumor DNA og karakterisere mutationer og epigenetiske forandringer heri. Dels at Stine Karlsen oparbejder laboratoriekompetencer til videreførelse i vores eget forskningsafsnit, både i eget projekt og kommende projekter. Desuden skal Stine Karlsen følge arbejdet i den kliniske afdeling på Royal Free Hospital, både i ambulatoriet og ved de multidisciplinære tumorkonferencer. Her forventes det, at Stine får et indgående kendskab til arbejdet med gastroenterologisk onkologi, idet de varetager behandling af både neuroendokrine tumorer og hepatocellulær cancer.

Eventuelt tøtte fra Novartis vil blive brugt til analyseudgifter, idet de genetiske analyser er omkostningstunge.
Vi tillader os at ansøge om 150.000,- Dkr, i henhold til vedlagte budget.
En kort projektbeskrivelse er vedhæftet.
På vegne af projektgruppen

Jens Kelsen
Overlæge, klinisk lektor, PhD

Circulating tumor DNA - patient-specific biomarkers for clinical decision support and tailored relapse diagnostics in neuroendocrine tumors

Study group
Stine Karlsen[1], Henning Grønbæk[1], Britta Weber[2], Elizaveta Mitkina Tabaksblat[2], Gerda Elisabeth Villadsen[1], Boe Sandahl Sørensen[3], Stephen Jacques Hamilton Dutoit[4], Jens Kelsen[1]

1: Department of Hepatology and Gastroenterology, 2: Department of Oncology 3: Department of Clinical Biochemistry, 4: Department of Clinical Pathology, all ENETS Center of Excellence, Aarhus University Hospital, Aarhus, Denmark

Background

Cancer treatment and surveillance is associated with significant costs. The challenge is to identify patients who are at increased risk of relapse or progression of disease.

Circulating tumor DNA (ctDNA), DNA with tumor specific mutations, can be found in peripheral blood in cancer patients [1, 2]. Monitoring amount ctDNA and its specific mutations, may be of value in risk stratification and clinical surveillance in neuroendocrine tumors (NET). Pancreatic NET is characterized by a well-defined pool of tumor mutations [3]. These mutations may predict survival and response to targeted therapy [4-7].

In small intestinal NET epigenetic changes has previously been reported [8] and is believed to have prognostic value.

Aims

To investigate whether the presence and characteristics of ctDNA can predict

- Relapse/progression in NET patients

We hypothesize that using ctDNA , we can identify patients that require special follow up. We further aim to correlate mutation profiles in tumor biopsies to ctDNA.

Materials and methods

We have collected samples from 70 patients with NET (G1-G3) of the pancreas (n=20) or small intestine (n=50) at our center. We collected blood samples when patients were newly diagnosed. Further we have purified DNA from tumor.
Purified DNA from plasma will undergo a specific tumor mutation profiling at baseline and the subsequent diagnostics will target the identified mutations.
Our samples will serve as a validation cohort for previous studies performed by the group at University College London/Royal Free Hospital.

Research plan, partners and collaborators

The project is part of Stine Karlsen's PhD project Aarhus University, and is approved by the Committee on Health Research Ethics in Denmark, the Danish Data Protection Agency and registered in www.clinicaltrials.gov: NCT02973204. The project has an interdisciplinary composition from the Aarhus ENETS CoE.
Purification of DNA from plasma will be anchored at Aarhus ENETS CoE. Subsequent tumor mutation profiling will be performed in collaboration with Christina Thirlwell, ENETS CoE at the Royal Free Hospital, London.
Christina Thirlwell has agreed to be the supervisor of Stine Karlsen during her stay at University College London during the first two months of 2019. We believe that this project will pave the road for a fruitful research collaboration between the two ENETS centers.

References

1. Yoon, K.A., et al., *Comparison of circulating plasma DNA levels between lung cancer patients and healthy controls.* J Mol Diagn, 2009. **11**(3): p. 182-5.
2. Bettegowda, C., et al., *Detection of circulating tumor DNA in early- and late-stage human malignancies.* Sci Transl Med, 2014. **6**(224): p. 224ra24.
3. Scarpa, A., et al., *Whole-genome landscape of pancreatic neuroendocrine tumours.* Nature, 2017. **543**(7643): p. 65-71.
4. Jiao, Y., et al., *DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors.* Science, 2011. **331**(6021): p. 1199-203.
5. Marinoni, I., et al., *Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors.* Gastroenterology, 2014. **146**(2): p. 453-60.e5.

6. Pipinikas, C.P., et al., *Epigenetic dysregulation and poorer prognosis in DAXX-deficient pancreatic neuroendocrine tumours.* Endocr Relat Cancer, 2015. **22**(3): p. L13-8.
7. Neychev, V., et al., *Mutation-targeted therapy with sunitinib or everolimus in patients with advanced low-grade or intermediate-grade neuroendocrine tumours of the gastrointestinal tract and pancreas with or without cytoreductive surgery: protocol for a phase II clinical trial.* BMJ Open, 2015. **5**(5): p. e008248.
8. Karpathakis, A., et al., *Prognostic Impact of Novel Molecular Subtypes of Small Intestinal Neuroendocrine Tumor.* Clin Cancer Res, 2016. **22**(1): p. 250-8.

Budget studieophold University College London og Royal Free Hospital, London 2019

Budget	Post	Units	Prize pr. unit (DKK)	Total (DKK)
Travel expenses				
	Airfare, train, bus, return trip DK-London	1	3.400	3.400
	Follow-up visit (travel, accomodation)	1	10.000	10.000
Total				**13.400**
Initial costs				
	Private and health insurance	1	4.000	4.000
	Establishing costs	1	5.000	5.000
	Work insurance	1	5.000	5.000
	Fee to university and hospital	1	5.000	5.000
Total				**19.000**
Living expenses				
	Accomodation, rent	2	20.000	40.000
	Local transport/month	2	750	1.500
Total				**41.500**
Operating expenses				
	Conferences	1	10.000	10.000
	Revision on statistics	1	10.000	10.000
	Revision of bioinformatics	1	10.000	10.000
	Publication fee	1	2.000	2.000
Total				**32.000**
Laboratory expenses				
	Utensils	1	10.000	10.000
	Laboratory technician	1	15.000	15.000
	Sequencing plasma DNA	140	400	56.000
	Sequencing DNA from biopsies	70	400	28.000
	Targeted DNA panel analysis	70	500	35.000
	Transportation of samples to/from UK	2	5.000	10.000
Total				**154.000**
Total (overhead not included)				**240.900**
Overhead (3%)				**7.227**
Total (overhead included)				**248.127**