Oncode Institute

Outsmarting cancer
Impacting lives

Strategic Plan

Prepared by Onco Research – July 2017

Version 3.1
Bruce Chabner
former director of the U.S. National Cancer Institute’s Division of Cancer Treatment

“...At the end of the decade, it was as if the whole discipline of oncology, both prevention and cure, had bumped up against a fundamental limitation of knowledge. We were trying to combat cancer without understanding the cancer cell, which was like launching rockets without understanding the internal combustion engine...."

"The Emperor of All Maladies: A Biography of Cancer"
by Siddhartha Mukherjee
Table of Contents

Preface .......................................................................................................................... 3

Executive Summary ...................................................................................................... 5

Vision, Mission and Objectives ..................................................................................... 10
  Vision: Outsmarting cancer, impacting lives .............................................................. 10
  Mission: to drive innovation through collaboration and get more out of science ........ 11

The Role for Oncode .................................................................................................... 13

Scientific Strategy .......................................................................................................... 15
  The research team ....................................................................................................... 16
  Research program ....................................................................................................... 20
  Core facilities ............................................................................................................. 36
  Building the research enterprise .............................................................................. 37

Valorization Strategy ..................................................................................................... 44
  The Oncode approach ............................................................................................... 45
  The valorization tools ............................................................................................... 54
  Valorization results ................................................................................................... 58

Organizational Structure and Governance ................................................................... 60
  Oncode – a virtual research institute ....................................................................... 60
  Relationship with principal partners ....................................................................... 61
  Organizational structure ............................................................................................ 63

Financial Plan ............................................................................................................... 72

Assessment and Monitoring Processes ......................................................................... 80

Glossary of Acronyms .................................................................................................. 86

The Oncode Manifesto .................................................................................................. 88
  Our Values .................................................................................................................. 90
Preface

It all starts with understanding

April 12, 2016. Matthijs van Nieuwkerk, the host of the famous Dutch talk show De Wereld Draait Door (The World Keeps Turning), welcomes five eminent scientists. All of them are specialized in fundamental oncological research, i.e. basic research on how cancer operates at the molecular level, with a focus on understanding the mechanisms of the disease. René Bernards, Anton Berns, Hans Bos, Hans Clevers and Jan Hoeijmakers announce a plan for a new, world-class institute that shall give a significant boost to the knowledge, prevention and treatment of cancer.

A heavy burden on society

Cancer is a devastating disease that places a heavy burden on society and individuals; it is one of the leading causes of death worldwide. In the Netherlands one out of three people are to be afflicted, sooner or later, by one of the conditions collectively called cancer. Understanding the molecular basis of cancer represents a solid foundation for developing more effective treatments. Strangely enough, although the Netherlands is a front-runner in oncology research, only few of the Dutch research findings have been the basis for new cancer diagnostics or treatments.

René Kuijten, member of the Topsector Life Sciences & Health, and Rudy Dekeyser, former Managing Director of VIB (Flanders Institute for Biotechnology) were convinced that some changes to the oncological ecosystem could result in propelling the Netherlands to a leading country in the translation of its research findings into products for the benefit of patients: invest in excellent fundamental cancer research with a long term perspective and simultaneously upgrade the valorization activities both in quantity and quality.

A new, innovative institute

Kuijten and Dekeyser started advocating that a giant leap forward could be taken by founding an institute based on two synergetic pillars. Firstly, unite the very best fundamental scientists in the field of oncology under one umbrella, with a joint mission and strategy, and provide them with long term financing to allow truly breakthrough research. Secondly, implement a top quality valorization strategy with the unambiguous objective to translate the research findings into novel diagnostics, new drugs and innovative treatments finally leading to more affordable effective health care and enhanced economic activity. With that idea in mind they approached some of the outstanding Dutch scientists (among them the ‘founding scientists’ mentioned above), KWF Kankerbestrijding (the Dutch Cancer Society) and the Dutch government. KWF Kankerbestrijding embraced the concept. So did three Ministries: the Ministry of Economic Affairs, the Ministry of Health, Welfare and Sport and the Ministry of Education, Culture and Science. They all agreed on a Memorandum of Understanding, in which they confirmed their
willingness to contribute financially to what we now call the Oncode Institute, provided that its strategic plan would meet their criteria.

But not only those funders were in favor of the plan. Several research institutes and university medical centers (UMCs), the latter supported by the National Federation of UMCs (NFU), showed their interest in joining Oncode. They became Oncode’s partner institutions.

**Onco Research: preparing the Oncode Institute**

Thanks to KWF Kankerbestrijding, especially its CEO, Michel Rudolphie, the preparations for the new institute could start. KWF Kankerbestrijding founded Onco Research, a temporary organization, set up to pave the way for Oncode. One of the main tasks of this temporary foundation was to formulate a strategic plan.

*And this plan is what lies in front of you.*

It is partly based on the experiences of the VIB, an excellent example in many ways. We have learned a lot from its experiences over more than twenty years. But the plan is also the result of discussions with lots of stakeholders and experts, among them the founding scientists, the funders and the partner institutions. We are grateful to all of them. Despite differences in opinions or interests – unavoidable if so many institutions and people are involved – they always kept the big picture in mind: outsmarting cancer, impacting lives.

Finally, we are thankful to Fred Plukker, former general director of Onco Research, for his dedication to getting Oncode launched and his involvement in the realisation of this strategic plan.

**Angus Livingstone – Valorization Director**
Executive Summary

Oncode Institute in a nutshell

A world-class institute

Oncode is a new, independent, world-class and innovative institute that unites, under a common strategy, more than five hundred of the Netherlands’ most outstanding scientists, specialized in the field of fundamental oncological research (i.e. research on how cancer operates at a basic, molecular level). Oncode incorporates the knowledge and experience to identify and foster scientific discoveries that are potentially beneficial to patients. The institute helps to pave the path leading from such discoveries towards translational and clinical research and practical applications. The institute fosters a climate in which contribution to valorization (the process of transforming knowledge into products, processes or services that are commercially feasible), is as highly esteemed as the scientific endeavor itself.

Working in close collaboration with partner institutions

The scientists collaborating within Oncode are, or will be, employed at one or more of Oncode’s partner institutions, at present: five UMCs, three research institutes and one university. With no research facilities of its own, Oncode operates as a virtual institute with a small staff consisting of a general support team and a team of valorization experts. In the near future, it is expected that other institutions will join Oncode.

Supported by dedicated funders

Oncode could not exist without proper financial support. KWF Kankerbestrijding, three Dutch Ministries (the Ministry of Economic Affairs, the Ministry of Health, Welfare and Sport and the Ministry of Education, Culture and Science) and our partner institutions collectively contribute in total €119 million over five years, with the provision for renewal after five years. The partner institutions deliver another €5 million in cash, along with a considerable contribution in kind, the latter in the form of deployment of scientific personnel and overhead costs.

What Oncode Institute stands for

Outsmarting cancer and impacting lives, that is our vision. Helping more patients survive, improving the quality of life for those afflicted, and ultimately curing cancer. We seek to achieve these objectives by driving innovation and getting more out of science. What Oncode stands for is better cancer treatment, faster. Excellence, both in the field of science and valorization, as well as collaboration is Oncode’s main characteristic.
A unique concept

Oncode is a unique concept that will enable significant oncological breakthroughs. The institute, supported by a public private partnership, links scientific excellence to (economic and social) valorization. It incorporates a joint, national research and innovation agenda that will be implemented through extensive collaboration, smart specialization and by sharing data and facilities. And finally, the concept includes a long-term funding strategy.

What is Oncode Institute

The first link in a long chain

For us, fundamental research is not a goal in itself. Oncode is part of a chain, part of an ecosystem directed towards the understanding, prevention and treatment of cancer. We find basic research at the very first stage of this ecosystem; the other stages – translational and clinical research, the development of products and services by industry and, finally, transferring those products and services to the market at affordable costs – are however as important. Oncode wants to speed up this whole time-consuming process.

A Dutch institute with an international perspective

Oncode is a Dutch institute with international aspirations. Its scientists are working together with colleagues all over the world. We seek collaboration with excellent oncological research institutes in other countries and will stimulate PIs, PhD-students and postdocs from outside the Netherlands to join Oncode.

How it works

Principal investigators

An elaborate process of bibliometric analyses (assessment of scientific publications) resulted in the selection of five outstanding Dutch scientists specialized in fundamental oncological research. Those five scientists (the ‘founding scientists’) guided the selection of an additional 38 Principal Investigators (including six junior Principal Investigators) all of them having excellent records. An additional 10-15 PIs will be selected in the coming years. The initial 43 PIs bring in their own research groups, totaling 560 scientists. These scientists are employed at nine institutions: AMC, Erasmus MC, Hubrecht Institute, LUMC, NKI, Radboudumc, Radboud University, Princess Máxima Center and UMC Utrecht.

Research program

The scientists affiliated with Oncode commit themselves to a common, integrated research program incorporating six themes, defined by the founding scientists: (1) development of novel technologies (2) understanding the critical drivers of tumor growths and the causes of resistance; (3) analysis of network perturbations in tumors and tumor-host interactions; (4)
causes and consequences of genetic instability; (5) identification of critical drug combinations and biomarkers for personalized cancer treatments; and, (6) mobilizing immune defense.

**Affordable health care**

Oncode feels a strong responsibility to contribute to affordable health care. We will optimize efficiency of costs during the first stage of drug development (discovery phase) and research, supporting the rationalized selection of participants in clinical trials. Furthermore Oncode aims to fund research to re-purpose abandoned and patent-expired or expiring drugs, and use these efforts to partner up with generic drug makers to develop highly innovative, but de-risked, drugs with relatively low margins.

**Base support and targeting funding**

Oncode will provide each of the PIs with a base research funding, €250,000 per senior PI and €150,000 per junior PI per year for five years. With this money the PIs can expand their research group necessary for executing the Oncode research program.

In addition, Oncode has at its disposal €30 million for five years for targeted funding. This money will not, like the base research support, be distributed equally over the PIs, but on the basis of plans that meet Oncode’s objectives.

**Translation to the clinic**

Oncode aims to bring fundamental research and the clinic close together. A considerable part of the targeted funds, €12.5 million over five years, is meant for clinical proof-of-concept activities: preclinical and translational projects and clinical studies. This will stimulate collaboration between fundamental, translational and clinical scientists. In order to maintain focus on the translation of fundamental research outcomes into products that are designed to the benefit of patients and society, we will also incorporate translational and clinician scientists in Oncode’s research management, valorization team and advisory committees. Society will be involved in guiding Oncode’s research through patient organizations, clinicians, industry and stakeholders.

**Valorization**

To foster greater impact from our research for the ultimate benefit of patients, Oncode is investing heavily in valorization (approximately €22 million over five years). We are fully mandated by the partner institutions for all valorization activities relating to Oncode researchers. Oncode will staff and operate a valorization team to provide dedicated support to scientists on topics such as business development, IP, translation to the clinic and entrepreneurship. Project costs will be paid from funds for IP protection, technology development and seed investment. Affinity to valorization will be one of the PI selection criteria and this will be stimulated by valorization training programs. Moreover, the research groups will be assessed on their contribution to valorization activities. The emphasis on valorization will not only accelerate the process from research to the clinic, but also leads to enhancement of
employment by offering work opportunities to scientific personnel, by facilitating startups and expansion of existing companies.

**How Oncode Institute is organized**

**Legal entity: a foundation**

Oncode is an independent foundation. The Supervisory Board counts seven members, including an independent chair. The UMCs, the research institutes, the Ministries and KWF Kankerbestrijding are each entitled to nominate a member. The other two members originate from the community of patients and industry.

**Internal structure: management and advisory bodies**

The Managing Board consists of a General Director, a Valorization Director and a part-time Chief Scientific Officer. The Chief Scientific Officer is the chair of the Research Management Committee that also includes the other four founding scientists, as well as a clinician scientist. The Research Management Committee advises the Managing Board on the contents and execution of the scientific strategy. The clinician on the team is also the chair of the Clinical Advisory Board.

Other relevant bodies are the Valorization Advisory Board, focusing on opportunities to translate new discoveries into clinical applications and new products, the Clinical Advisory Board, advising on the potential clinical value of scientific discoveries, and the International Advisory Board, which monitors the development and execution of Oncode’s strategy.

**How the money flows: financial forecast**

The road from a fundamental scientific discovery to an affordable health care product, happens to be a long one, fifteen years being no exception, with a high attrition rate. Though Oncode’s goal is to accelerate this process, it is not realistic to expect substantial results during the first five-year period of Oncode’s existence.

We forecast the revenues totaling €144 million in this first period: approximately €119 million provided by or related to the contributions by KWF Kankerbestrijding, the Ministries and the partner institutions, the remaining €25 million stemming from R&D industry funding, service rendered to third parties and intellectual property. Our expenditures include €64 million base support for PIs, €30 million for targeted funding (including the clinical-proof-of-concept programs) and €21.6 million for valorization-related expenses.
Next steps: Oncode in the future

Let us imagine what Oncode looks like twelve months from now. We picture an institute that is operational, though not yet fully completed. The funding is in place, the agreements between the Institute and the partner institutions have been signed. A considerable part of Oncode’s employees are recruited, including the members of the Managing Board and the valorization team. The base research support funds are at the disposal of the 43 PIs and a procedure for the selection of more PIs is submitted to the International Advisory Board.

Now it is time to start the next phase: extending the number of PIs. We expect to select an additional 10-15 PIs and their research groups, enhancing the number of researchers to about 866 by 2022. Those researchers will increasingly engage in valorization activities thus enabling Oncode technologies to be licensed and accelerating the development of those discoveries into the clinic. New companies will be created and international research partnerships will be formed. It is, in other words, time to pick the first fruits of the valorization ecosystem, though the real harvesting will take place in the second five-year period and even more so in the third one.
Vision, Mission and Objectives

Vision: Outsmarting cancer, impacting lives

Oncode wants better cancer treatment, faster. Our ultimate goal: helping more patients survive, improving the quality of life for those afflicted, and ultimately curing cancer. To this end, Oncode will take full advantage of the innovative power of the Netherlands. Advances in oncology can be realized more effectively when outstanding research is combined with first-class technology transfer. With such a combination Oncode will be securing the clinical and economic benefits for the Dutch society, leading to better cancer treatment:

- More effective diagnosis: Advance early-stage diagnosis of cancer or its risk factors, thus making cancer treatment more effective and less costly – or even preventing it altogether;
- More effective development: It will lead to faster development, and at higher success rates, of new, more effective medicines and other interventions;
- More effective treatment: Foster tailored treatment that improves patient recovery and quality of life, and replaces ineffective, but costly treatments.
Mission: to drive innovation through collaboration and get more out of science

Oncode has set the following strategic goals to accomplish its mission.

Scientific excellence

Oncode will focus on molecular cancer research that addresses both fundamental and clinically relevant questions.

Objectives

• Excellent fundamental oncology research and clearly adding value to the existing body of knowledge about the onset and the development and effects of cancer;
• Attracting and retaining the (future) leaders in cancer research and skilled scientists in areas essential to the fight against cancer;
• Establishing training, coaching and leadership programs for Junior PIs and postdocs that broaden their scientific, leadership and career skills;
• Implementing the principles of open access and the FAIR data (Findable, Accessible, Interoperable, Reusable).

Collaboration

Oncode will collaborate creatively fostering a culture of openness and sharing, to advance Dutch science and innovation in cancer research, thereby leveraging the Dutch oncology investments and bringing the world’s best research results to the Netherlands.

Objectives

• Support and fund novel and creative ways of interactions and collaborations between Oncode groups to accelerate the exchange of knowledge, research findings and data;
• Partner locally and internationally with UMCs, research institutes, universities and the wider oncology sector to provide access to leading research groups, facilities, equipment, data and unique environments;
• Involve society in guiding the Oncode research through involvement of patients, health practitioners, industry and other stakeholders;
• Support technology innovation and development for the entire Dutch cancer research community.
Valorization excellence

Oncode will create an integrated oncology ecosystem that efficiently links fundamental research with translational and clinical capacity, policy makers, national and international industry, and investors translating our research into clinical practices, medicines and other products to benefit patients and society.

Objectives

• Accelerate the development of discoveries that result in more effective, and affordable, cancer treatments, by:
  - making translatable science an integral and highly valued facet of our culture and education;
  - ensuring ideas and discoveries with potential for translation are identified and actioned quickly;
  - prioritizing public health objectives over financial returns in our patenting and licensing practices;
  - ensuring the connection to the clinic.

• Contribute to affordable health care, by:
  - optimizing efficiency of costs during the first stage of drug development (discovery phase);
  - stimulating research supporting the rationalized selection of participants in clinical trials;
  - funding research to re-purpose abandoned and patent-expired or expiring drugs;
  - creating strong positions in product development in order to be able to negotiate effectively with companies about bringing products to the market at affordable prices.

• Create value for the Dutch economy, by:
  - investing in the development of new technologies and products;
  - building close interactions with industry and develop durable partnerships;
  - creating, growing and retaining oncology companies in the Netherlands.

• Attract international investment (including foreign direct and venture capital investments) and research funding.

Please read more on Oncode’s vision, mission and values in our Manifesto and Values
The Role for Oncode

Oncode and the scientific, economic and societal environment

Cancer is a devastating disease that places a heavy burden on society due to its personal impact, costs to the health care system and lost productivity. The total economic impact of cancer in the EU was estimated at €126 billion in 2009. Partly due to the aging of the population, the impact is expected to increase in the future.

Recent scientific findings and technology have led to a revolutionary molecular approach to treating and managing cancer. This is key to the future of cancer treatment. Scientists have gained insights into the origins, growth and spread of tumors and now understand that cancer has many subtypes that react to treatment differently. Using molecular markers and DNA analysis, we continue to improve our ability in order to predict which patients will benefit from which treatments.

Globally, the race towards understanding molecular approaches is ongoing. Well-resourced teams in key centers around the world are making advances daily. The benefits of their work – better patient outcomes, new companies, and enhanced scientific performance – are accruing to their corresponding countries or regions. With a coordinated, sustained, well-resourced effort that builds on the existing oncology community and its achievements, the Netherlands is well positioned to become a global player in this arena and secure the resulting clinical and economic benefits for Dutch society.

Strengths and constraints in the scientific environment

Despite its small size, the Netherlands has been very effective in oncology research. Scientific output ranks third in EU in terms of numbers of peer-reviewed publications in oncology and related fields and fourth in EU in terms of citations. A strong network of excellent academic researchers from NKI, Hubrecht Institute and several Dutch UMCs have been already in place for the past 15 years under the auspices of the Cancer Genomics Centre (CGC) (www.cancergenomics.nl). First established with support of the Netherlands Genomics Initiative in 2002, in 2013 the CGC was designated as a ‘Center of Excellence’ and funded by a ten-year, €30.7 million grant from the Dutch Ministry of Education, Culture and Science (NWO Gravitation Program). This has resulted in a core of outstanding fundamental oncology researchers. Oncode is building on that foundation.

Through better understanding of the fundamental molecular mechanisms that underpin cancer, the research findings generated by this vital community provide the starting points for better cancer treatment. By integrating basic and clinical research, the UMCs and NKI provide the necessary infrastructure to support the translation of these findings into health solutions. Key translational infrastructure includes the Centre for Personalized Cancer Treatment (www.cpct.nl). Research from the NKI, for example, was translated to the breast cancer test MammaPrint®. Sold through the NKI spin-out Agenda, MammaPrint® has already helped over
50 thousand patients in 50 countries to find more effective treatment. Moreover, in 2014, over 200 clinical trials concerning cancer were performed in the Netherlands.

Despite its proven excellence and successful collaborations such as the CGC, the effectiveness of Dutch oncology research and translational environment can be improved further. This can be done by increasing collaboration between groups and by making expensive technology and expertise available, as well as by opening up infrastructure (such as biobanks, data repositories and patient cohorts) to a larger community.

An example of the level of collaboration that is currently required is the in-depth analysis of individual tumors: it requires sampling material from patients, establishing organoids (in vitro tumor cultures), DNA sequence analysis, RNA analysis, proteome analysis, metabolome analysis, drug profiling, functional studies, followed by bioinformatic integrations of the data and evaluation of the results using existing databases. A single research group cannot take all these steps by itself as it evidently lacks the required specific knowledge and expertise.

Oncode will be bringing more researchers, from all levels, into the active networks, which will ensure institute-wide access to the new enabling technologies, data and biological tools and help to forge partnerships with leading cancer centers worldwide.

**Bringing the key players together from funders and research institutes**

Oncode has brought the major stakeholders in the Dutch Life Sciences & Health sector together to ensure that Oncode’s innovations make a major contribution to Dutch health care and economy. The institute is supported by a public private partnership that brings together three Dutch Ministries (Economic Affairs; Health, Welfare and Sport; and Education, Culture and Science (including NWO and ZonMw)) and KWF Kankerbestrijding. Prominent research institutions in oncology – the NKI, Erasmus MC, UMC Utrecht, and the Hubrecht Institute – were initially involved in the establishment of Oncode. To strengthen the scientific position of Oncode, five additional institutions – LUMC, AMC, Radboudumc, Radboud University and Princess Máxima Center participate. In the future other institutions are likely to join. Finally, Oncode has the support of the Topsector Life Sciences & Health and the corresponding Regiegroep (steering group). They look for ways to strengthen the Dutch research base and improve its translation into economic activity and innovative products for patients.
Scientific Strategy

In this chapter we focus on the pillars of the scientific strategy.

- *The selection of outstanding fundamental oncology scientists for the research team*;
- The *research program with its six scientific themes*;
- *Oncode’s core facilities*;
- *Enabling growth and success by building the research enterprise through our*: 
  - people strategy;
  - research funding strategy;
  - technology strategy;
  - stimulation of open access & FAIR data;
  - clinical proof-of-concept fund for enabling clinical translation of the fundamental research; and,
  - building networks and collaborations.
The research team

The founding scientists

Oncode was conceived around the concept of bringing truly outstanding fundamental oncology researchers together. At the outset, using extensive bibliometric analysis, Oncode identified five of the top scientists in fundamental oncology in the Netherlands and invited them to provide scientific leadership for Oncode. The bibliometric analysis was conducted by the Center for Research & Development Monitoring (the ECOOM) at KU Leuven.

Based on the analysis, the following five scientists were invited to develop the scientific strategy for Oncode:

- René Bernards (NKI, Amsterdam)
- Anton Berns (NKI, Amsterdam)
- Hans Bos (UMC Utrecht)
- Hans Clevers (Hubrecht Institute / KNAW/ Princess Máxima Center)
- Jan Hoeijmakers (Erasmus MC, Rotterdam)

These scientists created the preliminary scientific strategy for Oncode, identified the outstanding fundamental oncology scientists active in the Netherlands to enable that strategy, and they will serve as founding members of the Research Management Committee. In addition to their scientific excellence, each of the founding scientists has a distinguished career in research leadership roles.
The initial scientific team

In addition, 38 Principal Investigators (including six junior Principal Investigators) from nine research institutions from across the Netherlands were invited to join Oncode’s initial scientific team (see Table 1). In proposing these scientists, the founding scientists used the following selection criteria:

1. impact for science, society and valorization;
2. relevance to cancer;
3. scientific complementarity;
4. technological uniqueness;
5. ability to collaborate;
6. vitality;
7. age; and,
8. gender.

An additional factor was the presence of a critical mass of excellent researchers and state-of-the-art infrastructure within each of their institutes. Each PI joins Oncode with his/her entire research group and commits to this Institute for at least the first five-year period. The 43 research groups of the initial scientific team will bring together over 560 scientists, including 180 postdocs, 180 PhD students, 20 senior scientists and 105 technicians, along with the corresponding support staff.

Growing the research enterprise

During phase I, Oncode aims to grow to 866 scientists. This growth is based on three contributing factors:

1. Selection of an additional 10-15 PIs and their teams during the first two years of operations. This will result in an additional 110 research staff;
2. The annual base funding provided to each PI (€250 thousand – senior PI, €150 thousand – junior PI) will enable the PIs to recruit additional researchers to their groups. With the average cost of a researcher estimated at €100 thousand per year, this will result in 120 additional research staff;
3. With the support of the business development professionals in the valorization team, we anticipate over €20 million in additional funding from industry, domestic and international granting bodies resulting in 60 additional research staff by year five of operations.
### Table 1: The initial scientific team and the involvement in Oncode’s six scientific themes

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<thead>
<tr>
<th>Principal Investigator</th>
<th>Research Focus</th>
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<td><strong>Netherlands Cancer Institute</strong></td>
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<tr>
<td>- Reuven Agami</td>
<td>Controlling cancer by RNA</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>- René Bernards</td>
<td>Functional cancer genetics</td>
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<td>✓</td>
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<td>- Anton Berns</td>
<td>Mouse cancer models</td>
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<td>- Thijs Brummelkamp</td>
<td>Experimental biomedical genetics</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>- Karin de Visser</td>
<td>Inflammation and cancer</td>
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<tr>
<td>- Jos Jonkers</td>
<td>Mouse models of breast cancer</td>
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<td>- René Medema</td>
<td>Cell division and cancer</td>
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<td>- Daniël Peeples</td>
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<td>- Ton Schumacher</td>
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<td>- Titia Sixma</td>
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<td>- Maarten van Lohuizen</td>
<td>Transcriptional repression</td>
<td>✓</td>
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<td>- Jacco van Rheenen</td>
<td>Intravital microscopy</td>
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<td>- Bas van Steensel</td>
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<td>- Lodewyk Wessels</td>
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<td>- Elzo de Wit*</td>
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<td>- Wilbert Zwart*</td>
<td>Hormone-associated cancers</td>
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<td>- Wouter de Laat</td>
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<td>- Puck Krijnscheer</td>
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* Junior investigators
+ co-appointed at Hubrecht Institute
Research team demographics

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Table 2: Age groups in the initial scientific team

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Table 3: Gender in the initial scientific team

- Overall gender distribution is 48.6% female/51.4% male
- Good gender balance at Postdoc, PhD and technician ranks. Women are under-represented at senior scientist and PI level.
- Geographic distribution: 45 nationalities: 64% Dutch, 21% European; 9% Asian; 6% other
Research program

Despite enormous progress in our understanding of the disease, the chance of long-term survival remains small for many cancer patients, particularly those with metastatic disease. Oncode will address this unmet clinical need through an innovative basic cancer research program. True innovation in the treatment of cancer relies on new insights into the basic mechanisms of oncogenesis, which in turn depends heavily on technological innovation. Oncode research will be guided by a number of key questions that need to be resolved to extend the life expectancy and improve the quality of life of cancer patients.

The principal scientific questions

We began by defining the principal scientific questions:

- Can we define new and better targets for therapy, based on detailed analyses of tumors, tumor-derived cell lines and organoids, and xenografts?
- What is the basis for tumor heterogeneity and how can we deal with this in cancer therapy?
- What is the role of the cell-of-origin on the tumor characteristics and responsiveness to therapy?
- How do cancer cells avoid host immune attack and how can we reverse this?
- How do non-mutated background genes influence tumor formation and response to therapy?
- Can we develop novel models to predict therapy response?
- How can we prevent metastatic disease?

The scientific themes

Based on these questions, the founding scientists have defined six scientific themes that create the basis for the integrated research program:

1. Development of novel technologies;
2. Understanding the critical drivers of tumor growth and the causes of resistance;
3. Analysis of network perturbations in tumors and tumor-host interactions;
4. Causes and consequences of genetic instability;
5. Identification of critical drug combinations and biomarkers for personalized cancer treatments;
6. Mobilizing immune defense.
Over the course of time the scientific strategy will be able to evolve naturally. Due to Oncode’s financial and valorization support the PIs and their research groups can adapt their research to changes in the environment. Oncode will stimulate researchers to be guided in their research direction by knowledge and experiences from clinical studies and patient experiences.
Theme 1: Development of novel technologies

Theme leader: Hans Clevers

Background

Discoveries in cancer biology are very much driven by the continuous development of novel technologies. These have enabled cancer biologists to study tumor evolution and complex cross-talk between various tumor cell subclones and the stroma, as well as mechanisms underlying therapy response and resistance, with ever greater resolution.

Theme aims

1. Single-cell technologies

Several Oncode researchers are developing single-cell technologies, which will be used to address the following topics:

Intra-tumor heterogeneity

To understand the role of tumor heterogeneity in clonal evolution of primary tumors, metastasis formation and chemotherapy resistance, we will develop technologies for simultaneous lineage tracing and single-cell multi-omics analysis of all individual tumor cells within primary tumors and metastases. We will analyze the clonal composition of the primary tumor and the corresponding metastases or resistant tumors by comparing the gene expression profiles of individual cells from each of the clones. We will expand this technology by combining single-cell lineage tracing with single-cell multi-omics analysis. For this purpose, we will develop methods to conduct simultaneous multi-omics measurements in single cells and live-cell imaging methods to simultaneously monitor expression of key cancer genes and cell fate in individual tumor cells.

Single-cell proteomics

UMC Utrecht will develop methods for single-cell proteomics using CyTOF technology. In this approach, cellular targets are labeled with metal-tagged antibodies and detected and quantified by time-of-flight mass spectrometry. Importantly, CyTOF analysis can be used for single-cell proteomics of laser-captured cells from tumor tissue sections. This approach will provide valuable information on the activity of key signaling networks involved in cancer (see Theme 3) at the single-cell level.

Single-cell metabolomics

Although the sensitivity of mass-spectrometry based metabolic measurements is not yet sufficient to reach single cell level, we will develop novel separation and purification methods to increase sensitivity to <1000 cells. In addition, we will develop various FRET based sensors to
measure key metabolites (e.g. glucose, pyruvate, citrate and lactate), which will enable us to combine microscopy-based single-cell metabolite measurements with the omics and imaging.

2. Organoids

Therapy selection

The Clevers lab has recently established a “living biobank” of long-term organoid cultures from a variety of primary human tumors and surrounding healthy tissue. This biobank will be expanded to provide an organoid encyclopedia of all major cancer types. Integration of multi-omic data (WGS, RNAseq, CNVseq, epi-genome, proteome) with data from high-throughput drug screens and other in vitro assays (including signaling pathway analysis and cell cycle/DNA repair analysis) will enable us to build comprehensive maps of pharmacogenomics interactions in cancer. These maps may be used to identify “biofacsimile” or “proxy” tumor organoids that most closely resemble the multi-omic tumor characteristics of individual patients. Moreover, the drug sensitivity profiles of these tumor organoids may subsequently be used to identify the most optimal therapy or combination therapy for these patients.

Cancer gene validation

To validate candidate cancer genes that enroll from genome-wide sequencing studies in human tumors, we will develop methods for CRISPR/Cas9-based modification of candidate cancer genes in cultured human organoids, which can subsequently be analyzed in vitro or in vivo upon orthotopic transplantation in mice. We have already successfully developed this technology for colorectal cancer, and aim to develop similar methods for all other major cancer types.

Drug resistance screens

We will use tumor organoids to perform in vitro drug resistance screens as well as in vivo screens in mice with organoid-derived tumors. To this end, we will transduce tumor organoids with genome-wide and focused lentiviral CRISPR, CRISPRi and CRISPRa libraries and identify target genes that confer resistance by next-generation sequencing of drug-resistant organoids/tumors.

3. Mouse models

We have developed several in vivo platforms for accelerated validation of candidate cancer genes in genetically engineered mouse models (GEMMs). These platforms include (1) CRISPR- or recombinase-based introduction of mutant alleles in GEMM-derived embryonic stem cells (ESCs), which can subsequently be used to generate new compound mutant mouse strains via blastocyst injection; and (2) CRISPR/Cas9-based in vivo manipulation of candidate cancer genes in non-germline GEMMs. We will use various CRISPR-based approaches (including CRISPR, CRISPRa and CRISPRi) to develop methods for more precise in vivo manipulation of target gene activity in germline and non-germline GEMMs. We will subsequently use these platforms to:

1. test comprehensive sets of candidate cancer drivers;
2. trace the cellular origin of cancer;
3. identify mechanisms of in vivo drug resistance;
4. determine the effects of genetic background to identify genetic modifiers of cancer initiation and progression.

4. Computational cancer biology

Develop approaches to identify important players in oncogenesis and therapy resistance

This entails mining large-scale tumor data sets for patterns that are associated with oncogenesis and therapy resistance. These include recurrence, mutual exclusivity and co-occurrence at the individual gene and pathway level. We will also focus on mining large-scale genetic screens (as performed in Theme 5) and developing approaches to robustly identify screen hits.

Mining drug response data sets

We will mine large-scale cell line drug response data sets such as the GDSC1000 as well as the growing sets of organoid panels to reveal combinations of biomarkers that predict drug response.

New computational approaches to model pathways in a semi-mechanistic fashion

This involves the integration of knowledge (pathway structure from Theme 2 and other sources) and multiple data types in order to explain drug response and reveal the mechanisms by which resistance occurs. We will extend these models to multiple cancer signaling pathways, and also model the decision mechanisms that integrate the pathway output and that give rise to relevant cellular states, such as proliferation, apoptosis and senescence. These models will be interrogated to reveal possible synergistic drug combinations. Model systems are similarly profiled at the single cell level (see above 1 Single-cell technologies).

Finally, we will adapt the approaches from 'Mining drug response data sets' and 'New computational approaches' mentioned above to develop novel approaches that are aware of population diversity and changes in time.
Theme 2: Understanding the critical drivers of tumor growth and the causes of resistance

Theme leader: Anton Berns

Background

Both genetic and epigenetic alterations are at the basis of tumor development and the acquisition of resistance to treatment. Also, the epigenetic make-up of the “cell-of-origin” may strongly influence tumor development. The challenge is to identify these critical genetic and epigenetic alterations and to understand the underlying biology in order to design more effective interventions.

Theme aims

1. Uncover drivers and causes of resistance with functional genetics

We will perform genome-wide gain- and loss-of-function genetic screens in vitro and in vivo using CRISPR/Cas9 technologies. These screens will be applied using operational in vitro culture systems including organoid cultures, as well as in vivo GEMM and PDX models of human cancer. These experiments should yield the driver genes (or combinations of genes) that are critical for tumor growth. Similar gain- and loss-of-function genetic screens in combination with drugs to which these tumors initially responded will be used to uncover drug resistance mechanisms. That knowledge will be invaluable to design combination treatments that can help to overcome these. Drug resistance mechanism caused by epigenetic alterations that are in principle reversible will receive specific attention. Furthermore, studying the epigenomes of healthy cells from which tumor cells originate will teach us to what extent the epigenetic make-up of cell-of-origin contributes to a particular drug response profile of the tumor cells. The data obtained from these functional screens will be integrated with data obtained from Aim 2/3 and subsequently validated in relevant in vivo tumor models (Aim 4).

2. Uncover driver defects in tumor samples with omics technologies

To uncover new critical driver lesions, we will determine the genetic alterations that occur over time during tumor progression as well as development of treatment-resistance in similar tumor subtypes. These studies will provide catalogues of somatic variants that will include both driver and passenger mutations. Importantly, the longitudinal sampling of well-annotated patient samples will allow us to study – with high precision – the clonal evolution and gains of mutations and epigenetic changes during the course of the disease. The deep sequencing of tumors using current technologies will enable us to determine whether mutations specific for resistant clones were acquired after therapy or were already present as minor clones at diagnosis.
Additional omics technologies, including transcriptomics, and proteomics (e.g. phosphoproteomics), will be used to systematically uncover the consequences of genetic and epigenetic alterations. Available and novel bioinformatics tools (Aim 3) will be applied to the patient samples (including longitudinally collected samples), and will assist in further classification within particular tumor types. Subsequent biological studies will be performed to gain further insight into the underlying mechanisms of tumor development and to identify putative novel therapeutic targets.

3. Development and application of bioinformatics tools for multi-omics defined drivers of transformation and therapy resistance

Using two different omics techniques has proven informative for identifying new driver lesions in tumors with similar tumor etiology. It is now being extended to pathway analyses and the inclusion of multiple omics techniques. However, we envision that these limitations will increasingly be resolved in the near future by improved technologies and further advances in integrated omics analyses. An important prerequisite for integrative data analysis is standardization of experimental approaches (sample collection and processing) and data formats. This will permit application of standardized integrative bioinformatics tools and coupling of data with public data resources and vice versa.

We will adopt the FAIR principles for all omics data at Oncode: Data should be Findable, Accessible, Interoperable and Reusable. This integrated analysis using newly developed bioinformatics tools on combined omics-derived data sets from large, internationally shared sets of tumor samples will help us to discover new putative therapeutic targets. It may also result in the identification of therapeutic targets across different tumor types that may not have been discovered or were assumed to be less interesting when studied only within a single tumor type.

4. Validate new drivers and assess underlying mechanisms of resistance in vitro and in vivo

The results of the first three aims will provide us with information about genetic and epigenetic abnormalities of specific types of tumors and their likely role in tumorigenesis and development of treatment resistance. To formally validate new drivers, either mutated genes or genes aberrantly expressed through genomic alterations or epigenetic mechanisms, gene-specific CRISPR/Cas9 gain or loss-of-function experiments using cell-based systems (tumor cell lines, organoid cultures (from both tumors and normal tissue stem cells) or iPSC models will be used to validate the new drivers and study how their tumor-inducing activity can be countered by specific combination therapies. Preclinical mouse models will be used, including advanced GEMMs generated by state-of-the-art technologies and PDX models. This will enable us to study tumor formation and treatment in a relevant in vivo context.

This will allow us to integrate the oncogenic consequences of specific mutations, epigenetic alterations, and the epigenetic ground state of the cell-of-origin. In selected cases, we will also look for specific background effects that we will try to align with the ever increasing information becoming available from Genome Wide Association Studies (GWAS).
Theme 3: Analysis of network perturbations in tumors and tumor-host interactions

Theme leader: Hans Bos

Background

To improve drug target choice and drug efficacy, detailed knowledge about molecular signaling networks at play and the network disturbances induced both by cancer inducing genetic lesions and by treatment is imperative. We will study networks ranging from minimal networks in purified protein complexes in vitro, to highly complex networks in dynamic tumor tissues in vivo, using high-end technology including (single cell) proteomics, metabolomics and high-end microscopy (cryoEM, Intravitral imaging).

Theme aims

1. Understanding the consequences and mechanism of disturbances at the molecular structural level using reconstituted protein complexes

Targeted cancer drugs and classical chemotherapeutics act upon specific proteins and/or DNA. By reconstituting defined systems, detailed mechanistic understanding of enzymatic reactions and their regulation can be achieved. Understanding mechanisms of regulation is resulting in novel targeting options. The defined reconstituted systems enable the effects of perturbations on network interactions to be resolved at the level of individual proteins and/or their interaction with other proteins or DNA. For this process, high-resolution structural information is imperative to improve drug targeting and to understand how molecular mechanism proteins are activated and/or inhibited. Moreover, detailed understanding of structures can explain how possible resistance is invoked. In vitro systems using purified proteins/protein complexes will be studied with a combination of biochemical, biophysical and structural methods: X-ray crystallography will be complemented by single particle electron microscopy to study the details of protein complexes relevant to networks involved in cancer progression and treatment.

2. Understanding cellular signaling networks: their interactions and the consequences of signaling network disturbances on network performance and outcome

Several signaling networks are inevitably disturbed in most, if not all, human cancers. These networks include the signal transduction pathways RTK-RAS, RTK-PI3K, WNT and TGFbeta, as well as pathways involved in maintaining genome stability. Oncode scientists are world leading in studying these pathways. In this aim we will study details on the regulation of these signaling pathways and the cellular fates that in turn are regulated by them (including, proliferation, migration/motility and metabolism) to discover new nodes in the networks of these pathways and their interconnections. We will focus on organoids as model system as this will enable us to study the role of these pathways in mediating individual cell behavior and cell-to-cell communication in the context of a heterogeneous tumor cell system. Single cell approaches
(CyTOF mass spectrometry, real-time imaging, super resolution and single cell RNA sequencing) will be used to determine the signaling status of individual tumor cells compared to their neighbors. We will focus on cancer stem cells and how their signaling fate is determined by the surrounding cells and vice versa.

Analyzing signaling networks following drug treatment to validate and develop the organoid system as a proxy for predicting patient response will combine the approaches mentioned above.

3. Identifying the cellular origin of tumor heterogeneity and understanding the role of cell interactions in cell behavior and drug response

Cells within a tumor are highly heterogeneous with respect to their phenotype and can manifest distinct morphological, molecular and functional features. Consequently, it is challenging to design treatment therapies that target all cancer cells with equal effect. We will study the heterogeneity of cellular behavior during cancer growth and therapy resistance in human cancer samples. Among other aspects, we want to identify and characterize the origin and nature of the resistant cells that give rise to cancer recurrence. To that end we will introduce biomarkers that track the fate of tumor cells. As model system we will use tumor organoids both in vitro and transplanted in mice. High-end microscopy using fluorescent proteins will be used to monitor plasticity over time, and single-cell analysis (DNA/RNA, Cytof and mass spectrometry) will be used to characterize the various cell types in additional detail, both in the presence and absence of perturbing drugs or after CRISPR-mediated DNA manipulation.

4. Understanding the interactions between tumor cells and their environment/microenvironment

Within the tumor mass, various cell types interact (including cancer stem cells, quiescent cells and dying cells), thereby determining cell fate in an interactive manner. This network can be extended by taking into account the tumor environment and microenvironment, consisting of metabolites, cancer associated fibroblasts (CAFs), immune cells, endothelial cells and other components. We will study the interaction of the tumor mass with the microenvironment by extending the organoid culturing system towards co-culture systems with which this environment/microenvironment is mimicked at least in part. As with the other aims, the contribution of environmental factors to tumor fate and tumor cell signaling networks will be studied. In addition, by transplanting tumor organoids into mice we can validate and extend the role of network disturbances and the role of the environment/microenvironment in this process, also in a complete organism. To complement these studies in models with an intact immune system, syngeneic and genetic tumor mouse models will be used. Intravital imaging combined with labeling of signaling components in individual cells will be used to track cell fate following various interventions.
Theme 4: Causes and consequences of genetic instability

Theme leader: Jan Hoeijmakers

Theme aims

The general aims of this research theme are to understand the causes and consequences of genomic instability, the contribution of genomic instability to cancer, and the potential of using genomic instability in novel strategies for patient stratification and therapy. This leads to four specific aims with associated research questions that range from molecular mechanisms to therapeutic strategies:

1. Molecular mechanisms that protect genome stability

How is detection and repair of genomic damage performed and regulated, and how is regulation of cell cycle progression coupled to these processes?

The focus will be on chromosome segregation and the DNA damage responses (DDR) in relation to genomic insults and replication/transcription stress and chromatin context. We will use a range of state-of-the-art molecular and cellular approaches, including:

- single-molecule biophysics/imaging;
- biochemical reconstitution and structural biology;
- x-link proteomics;
- high resolution/super resolution imaging of subcellular processes including dynamics of protein recruitment to, and protein/protein interactions at, specific locations,
- genetic tracings of damaged loci; and,
- genetic and proteomics screening to uncover players and functionally relevant interactions/modifications.

All of the above approaches will be coupled to sophisticated abilities to perturb protein function in conditional ways (e.g. conditional knock-out/protein degradation and optogenetics).

2. Mechanisms of genome instability in cancers

Which forms of genetic instability exist in which cancers, and what are the underlying molecular defects or contributing factors? Which non-cell autonomous factors impact genome instability or survival of genomically unstable cells? Which predisposition genes affect genome integrity and how?
The efforts will focus on using specialized read-outs of distinct genome stability processes for assessing defects in cancer tissues, such as patient-derived tissue slices, PDX models and tumor organoid cultures. The read-outs include:

- **fixed, live cell and intravital imaging of DDR responses and chromosome segregation, such as live fluorescent assays of DNA damage detection and repair, and spindle assembly, chromosome-spindle attachment, error-correction and spindle checkpoint signaling;**

- **genome-wide genetic tracing of the appearance and fate of double-strand breaks.**

The influence of age and micro-environments on the ability to maintain genomic stability will also be studied.

### 3. Role of genome instability on cancer initiation, development and progression

How genomically heterogeneous are various cancers, and does this heterogeneity change during development? When do the various forms of genome instability arise? How do they impact tumor initiation/development/progression, and does this differ between tissues, ages and the moments at which instability arises? How does the level of instability affect fate of nascent tumor cells?

Single-cell sequencing technologies and patient-derived tumor samples/organoids will be used to determine the level of genomic heterogeneity in patients, if possible at different stages of tumor development. This will enable a thorough evaluation of the modes of tumor evolution. Sophisticated, conditional animal and animal-free models, such as organoid cultures with patient-relevant perturbations to genome stability processes, will be generated to determine the contribution of various forms/levels and timing of instability to tumor development. Genomic and imaging-based lineage tracing experiments will enable long-term tracing of the fate of genomically unstable cells.

### 4. Increasing genome instability as cancer therapy

What is the mechanism of action of classical anti-cancer drugs that target DNA or the spindle? What determines sensitivity/resistance to these drugs and to other treatments such as radiotherapy? Can we identify additional druggable targets in the genome stability pathways? Can we develop robust approaches to efficiently determine synthetic toxicity and/or synthetic lethal genome stability interactions in specific cancer cells? Can we improve immunotherapy approaches by targeting genome stability pathways?

The models described under Aim 3 will be used to screen for enhancers/suppressors of drug sensitivities to uncover predictive biomarkers for drug response/radiotherapy and to test new treatment strategies (including immunotherapy) aimed specifically at cells deficient in specific genome stability pathways.
Theme 5: Identification of critical drug combinations and biomarkers for personalized cancer treatments

Theme leader: René Bernards

Background

We will focus on the identification of novel drug targets and drug combinations using gene inactivation and chemical compound screening technologies. These analyses will be carried out in all model systems available within Oncode: cell lines, organoids, PDX models, GEMMs and human tumor explant cultures. A more specific focus will be on drugs that have limited (or no) clinical efficacy as single agents. Through synthetic lethal screens, we will search for more effective combinations with these existing agents. In addition, we will employ modern technologies to study the biology of existing effective anticancer drugs. The chemical space around these molecules will be explored to find novel anti-cancer activities with reduced toxicity for patients. The biology of these activities will yield biomarkers of genes actively involved in the drug biology and will be explored as biomarkers for more personalized treatments.

Theme aims

1. Identification of novel combination therapies for cancer based on identification of synthetic lethal interactions

We will use targeted cancer drugs that have limited clinical benefit to perform genetic synthetic lethality screens to find enhancers of the responses to these drugs. A particularly interesting group of drugs are those that have been abandoned because of lack of single agent activity in the clinic. Such drugs may have been needlessly abandoned and might be revived through synthetic lethal screens to find effective combinations. We will obtain these drugs either directly from companies or after a search in the patent literature and resynthesis of the drugs. This will yield unique, high quality drug libraries that will be broadly distributed in Oncode for further study.

2. Identification of context-dependent drug targets: drug targets that are toxic only to cancer cells having a defined genetic lesion

In this aim, we will select undruggable cancer mutations and search for their associated vulnerabilities with the ultimate goal of designing specific therapies for tumors having these mutations. The identification of the underlying biology may yield new targets for manipulation and may also yield biomarkers for treatment prediction. These findings will then be tested retrospectively in the large data sets available at Oncode, followed by prospective studies.

3. Identification of novel components of major cancer-relevant signaling pathways that can serve as novel targets to modulate these pathways

There are some 10-15 major signaling pathways that are perturbed in cancer, and many of these pathways contain nodes that can be targeted by drugs to treat cancer. However, there are still
unknown components of these cancer-causing pathways that need to be mapped. These ‘new’ players could also be excellent biomarkers for predicting responses to the selected drugs. We will use genetics in cultured cells to identify such missing pathway components. To do so, we will use a recently developed approach in which mutagenized cells are stained with antibodies to measure pathway activity. Subsequent cell sorting and DNA sequencing will generate overviews of regulators affecting the measured pathway. This approach will be applied to all major signaling pathways that are deregulated in cancer or targeted by therapeutics. Using a similar approach, we recently identified a new off-switch in the AKT signaling pathway as well as a “missing” enzyme affecting the cytoskeleton.

4. Identifying acquired vulnerabilities of drug-resistant cancer cells

A widely-held hypothesis is that development of drug resistance leads to tumors that are more difficult to treat than the original drug-sensitive tumor. We will therefore focus on finding acquired vulnerabilities of drug-resistant tumors. These acquired vulnerabilities may be even more significant than the original vulnerabilities of the untreated cancer. To define new resistance mechanisms, we will use genetic screens coupled to expression information on human tumor cells and tissues that have become resistant. These could subsequently be used to selectively target resistant tumor cells with fewer bystander effects on normal healthy cells.

In general, the outgrowth of drug-resistant subclones should be prevented, both those already present at primary diagnosis (intrinsic resistance) and those which became mutated during exposure to chemotherapy (acquired resistance). We will focus on the dynamics of clone/subclone development in relationship to drug resistance and will study ways to interfere with mutated clones/subclones or to sensitize them to drugs or drug combinations (novel or existing).

5. Development and use of organoid-based model systems to study drug response

Organoid technology has the advantage of testing primary tumor cells and has a higher likelihood of identifying relevant targets (including druggable targets). We will develop organoid culture systems and combine these with CRISPR-Cas9 technology to correct and introduce specific cancer mutations to generate modified cancer genomes of interest. This will enable the effect of single cancer mutations to be evaluated regarding drug response, therapy resistance, invasiveness and other factors. We previously found that normal colon organoids with a mutant KRAS have similar resistance to targeted drugs as tumor organoids with mutant KRAS. We will use these “isogenic” models to identify vulnerabilities that can be directly related to specific mutations, rather than the complex genomic background of a tumor organoid or an ill-defined cell line. The results will be evaluated in vitro in multiple available tumor organoid panels. Intravital imaging of transplanted tumor organoids will be used to study the mode of action of drugs in vivo.
6. Defining the cell biology of established anti-cancer drugs

Various older drugs are still effective, but have substantial toxicity. The mode of action of these drugs was usually determined decades ago, and we have shown for one such a drug that re-analysis of the drug activity may show additional anti-cancer effects. These can then be explored with the objective of eliminating these toxicities through drug synthesis and exploring the chemical space around the drugs to define new treatment options. We will explore the biology of these drugs by using cell biological tools in combination with pull-down experiments of chemically modified drugs that allow introduction of an isolation handle, and through further screening. These older drugs include the anthracyclines, cisplatin and variants, taxol, anti-estrogens, anti-androgens, glucocorticoids, and anti-metabolites, and many more drugs that in fact represent the bulk of anti-cancer treatments to date. Improved understanding of the biological activities of drugs will yield new candidates for personalized treatment, drug variants with lower toxicity and/or methods to predict undesired toxicities.

To monitor clinical effects, we will continue developing the analysis of circulating tumor cells and circulation tumor DNA and RNA, an application that will be combined with organoid technology. To modify drugs, we will use chemistry.
Theme 6: Mobilizing immune defense

Theme leader: Ton Schumacher

Theme aims

The general aim of this theme is to identify new generation cancer immunotherapy targets and cancer immunotherapies through mechanistic analysis of the immune system, either in isolation or in its interaction with cancer cells. The theme has three specific aims.

1. Dissection of fundamental mechanisms of immune regulation and immune responsiveness

The central focus of this aim is to identify and characterize novel immunological checkpoints that influence anti-tumor responses. The concept of “immunological checkpoint” should be interpreted here in the broadest sense, not only involving classical receptor-ligand interactions, but also metabolic checkpoints (e.g. hypoxia, lactic acid accumulation and glucose deprivation), epigenetic states of immune cell exhaustion, and a possible role of the microbiome.

The mechanism of action of these pathways and the cells they control will provide basic insight into tumor immune surveillance and failing anti-tumor responses. Such knowledge will be essential for future development of novel immunotherapeutic strategies that lead to elimination of cancer cells while causing minimal collateral damage. Approaches to reach this goal include fundamental analyses of the role of presumed checkpoints in preclinical models, and the development and use of genetic screening approaches to identify immune modulators in either in vitro systems or mouse models.

2. Understand the tumor-promoting effects of immune cell subsets

The central goal is to obtain mechanistic insights into the enhancement of tumor progression and metastasis formation by immune cells, in particular myeloid cells. We are interested in understanding how cancer cells shape their local and systemic immune environment to their own benefit, and whether and how this process can be reversed. Using various genetically modified mouse models for cancer and cancer patient specimens, we will examine how the genetic make-up of tumors dictates their crosstalk with the immune system. In addition, we also test to what extent classical cancer therapies reshape such crosstalk. Finally, we will dissect the impact of tumor-educated myeloid cells on the efficacy of cancer immunotherapies and classical chemotherapeutics. Besides having access to advanced mouse models and patient sample series, this aim will benefit from imaging expertise (intravital microscopy) to visualize cellular interactions (an area where further technology development will likely prove of value) and bioinformatics expertise to untangle the networks between tumor-resident cellular subsets.
3. Understand the mechanisms of intrinsic and acquired resistance to present-day cancer immunotherapies

Our primary objective is to understand which factors limit the activity of present-day cancer immunotherapies, and how we can overcome these constraints. In this context, three areas of importance need to be distinguished. First, while current checkpoint blockade therapies show profound activity in patients with melanoma and mismatch repair-deficient cancers, clinical activity in many other human tumor types is modest. Second, while many clinical responses seen upon cancer immunotherapy are durable, some of the patient's relapse, and the causes of relapse are largely unknown. Dissection of such intrinsic and acquired immunotherapy resistance mechanisms will very likely contribute to the development of novel biomarkers, and also to novel strategies that convert a non-responsive into an immunotherapy responsive tumor. Third, the benefits of current checkpoint blockade therapies come at the cost of adverse events, which are often severe and possibly chronic-immune related. Understanding the cause of these events and the risk factors for developing them will assist in selecting the therapy of choice for patients and greatly improve quality of life. This can entail blockades of other, novel checkpoints used in a tumor-specific and/or patient-group-specific setting.

Experimental approaches that will be used to understand therapy resistance include analysis of tumor micro-environments (murine and human), functional analyses of tumor material, and analysis of resistance mechanisms through genetic screening systems. The latter includes the development of physiologically relevant in vitro and in vivo systems for systematic large scale genetic perturbations. Development of robust high-throughput systems for single cell sequencing would also contribute substantially to this aim.

Knowledge obtained in these analyses will form the basis for designing therapies that can overcome such intrinsic or acquired immunotherapy resistance. Depending on the defect identified, such mechanisms include: A) development of vaccines (in case of insufficient immune priming), B) combination with chemotherapy and radiotherapy (in case of insufficient intratumoral inflammation and/or immune priming), and C) development of small molecule or antibody inhibitors (in case of checkpoints shown to limit activity of current immunotherapies). In parallel, knowledge obtained can be exploited for the development of biomarker-based algorithms for patient stratification.
Core facilities

Oncode and the participating institutions will provide the following core facilities required for executing the Oncode science program.

1. Most of the essential facilities are present in all partner institutions, either under the direct supervision of Oncode’s PIs, or with direct access for Oncode’s groups.
   - mass specs for proteomics and metabolomics;
   - state of the art mouse facilities;
   - high throughput functional genomics tools and analysis pipeline;
   - a large variety of (high-end) light microscopes, including light sheet microscopy and super resolution microscopy;
   - bioinformatics support;
   - clinical trial units (for collaborative clinical trials).

2. Some of the facilities are only present in one or two partner institutions and can be accessed through collaboration.
   - the NKI functional genomics core. This facility provides the CRISPR, CRISPRi and CRISPRa libraries required to perform functional screens in the context of this program;
   - UMC Utrecht’s Metabolomics core;
   - Hubrecht Institute & NKI: Intravital imaging. This unit provides support in the intravital imaging studies using drug combinations in various mouse models;
   - LUMC: Chemical synthesis;
   - Hubrecht Institute: Single Cell RNA sequencing;
   - NKI and Radboudumc facilities for GMP for drugs and biologicals (for early translation to patient trials);
   - Hubrecht Institute Organoid Technology foundation for organoid bio-banking.

3. Large facilities relevant for Oncode groups.
   - NKI Mouse facility. This unit provides support in generating genetically engineered mice using CRISPR/Cas9 and GEMM-ESC technology;
   - Hartwig Medical Foundation for whole genome DNA sequencing;
   - structural biology facilities for cryoEM (UMC Utrecht) and NeCEN (LUMC) and X-ray crystallography (ESRF, SLS);
   - cooperation with BBMRI (Biobanking and BioMolecular resources Research Infrastructure The Netherlands) and Health RI (Research Infrastructure).
Building the research enterprise

Oncode will create an environment that supports the growth and success of the research enterprise. Oncode will grow by implementing an integrated strategy around people, research funding, technology access, communication, networks and valorization and by fostering the success of our community of researchers and our network of stakeholders.

People strategy

Exceptional outcomes stem from recruiting the best and the brightest people, and providing them with the support required to reach their maximum potential. Oncode aims to inspire a constant flow of knowledge to a new generation of scientists, valorization experts and support staff. The aim is to be diverse, welcoming talent of all backgrounds. We will support researchers at all stages of their careers, from PhD to senior PI. Oncode will create a training program, tailored to inspiring researchers and equipping them with the confidence and tools to create breakthrough impactful innovations. Together advancing the field of oncology in the Netherlands and abroad.

Stimulating environmental factors

Attracting and retaining excellent researchers requires a special environment in which the researchers are able to focus 100% on their research. Important elements that contribute to this are sufficient core funding for an extended period, access to adequate infrastructure and the best technologies, as well as a dialectical culture and incentives for cooperation. Oncode will focus on selecting and retaining researchers with the best international ranking or potential, a good balance between stability and renewal and a healthy mix between international and Dutch talent.

United against a divisive enemy

Effective cancer research is unthinkable without collaboration. We will foster a culture of sharing knowledge. The longstanding principles of individual success have become obsolete. You don’t own success; you help build it.

We adopted the principles of open access and FAIR data, and knowledge translation will be strongly supported. The Institute shares new insights and developments with funders and the scientific community. Learning from patient stories and openly sharing its progress and findings, Oncode aims to promote science in a new way – one that is transparent and inspirational. Oncode will create a virtual platform for collaboration and debate. A digital communications platform will be established to enable better communications within Oncode and with its external communities.

We believe that a culture of sharing knowledge by virtual teams cannot be established without face-to-face interaction. We aim to bring the Oncode scientists together, for example at the Oncode Annual Scientific Meeting. The aim of the annual meeting is to inspire, share and excite.
While the primary purpose is the scientific exchange, it will also provide a venue for short courses, stakeholder engagement, sharing Oncode’s strategy, plans and celebrations. For this meeting the scientific community, research partners, industry and patient organizations will be invited. Oncode will sponsor the participation of all postdocs and PhDs.

**Program elements:**

**Training program – aimed at all levels**

Specific programs will be customized to the needs of PhD students, postdocs and PIs. The goals are to grow the innovative potential of the research teams, stimulate leadership competencies and help to create new paradigms for coexisting among scientists. We trust this will lead to attracting even more top candidates, enhancement of educational experience, improvement of employability and the creation of a more cohesive team environment across Oncode. The program will offer a combination of short courses, workshops and seminars, both in-person and online. General categories include innovation, leadership and coaching, scientific tools and techniques and personal skills. Specific topics could include:

- introduction to technology transfer;
- introduction to clinical research;
- research ethics;
- data access and management;
- leadership for postdocs;
- preparing for a grant interview;
- communicating science to the public;
- (emerging) technology (see Technology strategy below);
- building effective stakeholder relations.

**Physician-scientists recruitment & training program**

Physician- and clinician-scientists are crucial to foster ever more powerful translational research and to enhance awareness of clinical relevance at all levels in the laboratory. We will develop a program to attract and train physician-scientists. We will stimulate physician-scientist’s participation in Oncode’s laboratories as PhD candidates or postdocs, and support them with training programs inside and outside the laboratory - where possible, in partnership with our partner institutions.

**Female investigator program**

This program is aimed at young female researchers who have completed their post-doctoral training with distinction and are just starting their career as an independent PI. Up to eight awards of €150,000 per year will be granted for a period of five years. Naturally, these PIs are also eligible to access Oncode’s supplemental research funds, training & coaching programs and
they will receive full support of the valorization team to help them establish their research programs.

**Mentoring program**

The ability to innovate at the highest level will depend upon the new generation of investigators receiving outstanding mentoring from their senior scientific colleagues. Oncode will institutionalize a program to engage the current scientific leaders to become mentors to support the Oncode millennial generation in their quest to drive a breakthrough change. Scientists will be matched with mentors on the basis of their personal endeavours, cross-fertilization between institutions and research themes. The current senior scientific leaders will actively participate in the creation of the mentorship program.

Oncode’s valorization team (details in next chapter) provides business development, IP management and stakeholder management support, combined with hands-on mentoring. Supplemental funds are available to support IP management, technology development, clinical proof-of-concept and seed investment. The valorization team will have a strong network into the relevant communities to help accelerate the development of opportunities.

**Anticipated growth**

During Phase I (2017-2022) Oncode anticipates a growth of 60%, from 560 to 866 researchers. We aim to attract the best and brightest. Selection of the new PIs will be done through a formal application procedure, open to candidates from all institutions – domestic and international. We have not established the full selection criteria yet, but they will be based on Oncode’s vision, objectives and values: scientific excellence, experience and commitment towards valorization, translational and clinical research experience and collaboration. These selection criteria will be transparent, measurable and assessable. The application procedure will include a process for formal peer review. Special consideration will be given to recruiting female scientists, international scientists and fundamental molecular cancer research-trained physicians. Oncode will recruit at least two PIs with a focus on translational research.

The intended recruitment criteria and the selection process will be reviewed by Oncode’s Research Management Committee and the International Advisory Board and has to be approved by the Supervisory Board. Furthermore, the Supervisory Board will supervise the selection process and procedure as a whole.

**Research funding strategy**

The estimate of the current level of annual research funding to the initial 43 PIs is estimated at €60 million (including in kind contributions of partner institutions and competitive grants). By the end of Phase I, total research funding is expected to increase to €95 million based on:

- the funding that comes with the recruitment of 10-15 additional PIs and their groups;
- research funding provided by Oncode (€18 million by year 5); and
increased externally funded research (€7.5 million by year 5).

Oncode will provide its PIs with annual base level of funding of €250k (€150k for junior PIs). Funding is provided for five years, subject to adherence to Oncode’s scientific plan and annual review. In addition, PIs will gain access to Oncode’s supplemental programs and targeted funding in order to promote collaboration, internationalization and enhance the research capacity and effectiveness of researchers (€6 million per year for Equipment and Infrastructure, Clinical proof-of-concept, Technology Access, Institutional & International Initiatives).

Being an Oncode research group means that a substantial proportion of the research program of the group falls within the scope of Oncode’s research strategy. PIs retain full academic freedom to pursue their own scientific interest and are not required to restrict their research exclusively within the field of oncology.

The research groups follow Oncode’s policies, for example regarding data sharing, open access, access to facilities and intellectual property.

The PIs will report to Oncode on their scientific progress and accomplishments (see Assessment and Monitoring Processes).

In exceptional cases, Oncode has the right to suspend or terminate funding to a partner institution or a PI, such as in the event of scholarly misconduct, fraudulent or criminal activity or failure to provide adequate reporting.

Technology strategy

To enable world-class research and attract/retain leading researchers, Oncode must provide scientists with access to next generation technologies and the training and support to use these effectively. This enables scientists to answer research questions faster and more effectively.

The pace of technology development is accelerating and outstripping the ability for researchers to stay on top of technology advances, affording access to them and integrating them into their research programs. Recent examples include next generation sequencing, organoids and Crisper-Cas9 technologies. The costs are prohibitive, not only in terms of procurement, but also in terms of installation, training and operations. Besides being expensive to buy and install, they are challenging to learn how to be used effectively and efficiently. In some cases, they generate extraordinary amounts of data creating or exacerbating the challenges of data storage, integration, processing and standardization. As a result, access for individuals is rarely affordable or cost effective.

Program elements

Technology access program

The technology access program is designed to provide Oncode researchers’ access to emerging technologies. The program will scan for emerging technologies and conduct preliminary assessment on their potential values. The technology access fund (€500 thousand per year) will
support accessing technologies and validating their utility and effectiveness. The program will be managed by four PIs with high affinity for technology and one valorization business development officer.

Technology access fund:

- **€200 thousand budgeted per year to access candidate disruptive technologies.** 
  Internationally developed but still not commercially available. Typically provide up to €20 thousand;

- **€300 thousand budgeted per year to support projects in using recently commercialized technology (< 2 years).** Typically, €10 thousand - 20 thousand per project – co-funded 50:50 with PI;

- **all programs require cooperation on development of case studies and presentations at the seminar/annual meeting**;

- **direct connection to the Oncode Training Program.**

**Technology development**

The technology development fund (€1 million per year) targets inventions and technologies developed by Oncode researchers with the aim of reducing technical uncertainties, increasing value and advancing them to a stage where we can attract additional development funding to continue development or option/licence to a third party. Projects are intended to demonstrate proof-of-concept, develop prototypes, broaden/strengthen patent claims, conduct external market studies, address critical scale-up issues and conduct critical pre-clinical studies. Individual projects will range in value from €10 to €150 thousand and where possible, external funds will be used to cost-share and augment project funding.

The technology development fund will be managed by the valorization team with the support of the Valorization Advisory Board.

**Equipment and infrastructure**

The equipment and infrastructure program (€2 million per year) targets larger equipment and infrastructure projects, supporting broader access to key scientific capabilities that are more cost effective when shared (i.e. expanding sequencing capacity, omics data storage and processing, imaging facilities and model systems facilities).

The following general terms apply:

- **projects must support the needs of multiple PIs**;

- **quarterly call for proposals**;
• resulting facilities/equipment must be available to all Oncode researchers;
• project selection adjudicated by Oncode’s Research Management Committee;
• awards > €200 thousand require external review.

Oncode training program

As outlined in the People strategy, the Oncode training program will offer short courses and workshops in a number of areas, including scientific tools and techniques. This program will create a regular forum for exposing the broader Oncode community to new technologies, including case studies, operational training, and if required, certification.

Open access & FAIR data

Oncode supports widespread access to our cutting-edge research and knowledge in order to enable researchers, scholars, clinicians, policymakers, private and not-for-profit organizations, as well as the public, to use and build on this knowledge.

Oncode therefore promotes the availability of findings that result from our research, including research publications and data, to the widest possible audience and at the earliest possible opportunity, by:

- Adopting the widespread dissemination of Oncode’s research results by open access to all of Oncode researchers’ publications. Supporting open access enables our researchers to make their publications freely available to the international research community and to the public at large, thereby enhancing the use, application and impact of research results.

- Enhancing good data management of Oncode’s research data by adopting the FAIR data principles - a set of guiding principles to make data Findable, Accessible, Interoperable, and Re-usable. Good data management supports knowledge discovery and innovation and subsequent data and knowledge integration within Oncode. Thereby, it enables reuse by the community after the data publication process.

Clinical proof-of-concept

The clinical proof-of-concept fund (€2.5 million per year) is available to enable clinical translation of Oncode’s fundamental research. Funding is available for pre-clinical projects and translational projects that have a clear clinical goal, and especially for clinical proof-of-concept studies. These latter studies will be instrumental to validate the concepts developed in Oncode’s fundamental research and facilitate their transition into the clinic. Up to €250 thousand will be available per proof-of-concept clinical study initiated by clinical investigators that collaborate with Oncode PIs to demonstrate clinical validity of discoveries made by Oncode PIs.
The following general terms apply:

- *projects must be tied to an Oncode discovery;*
- *the lead clinician may be associated with any Dutch institution;*
- *funding decisions are adjudicated by the Research Management Committee (senior clinician scientist);*
- *projects > €200 thousand require external review.*

**Building networks & collaborations**

Oncode is part of a larger international oncology community and value chain for new innovations. We will build relationships with national and international oncology research centres and institutes to supplement and enhance the capacity of Oncode researchers. Facilitating Oncode researchers’ access to tools, data, specialized facilities and scientific expertise, will allow Oncode to leverage external capacity, reducing both time and costs. We will provide funding dedicated towards facilitating research collaborations at both institutional and PI level.

In addition, Oncode will seek possibilities to partner with external organizations to enhance the breadth and cost effectiveness of its own programs, such as the training programs, valorization initiatives (management of our seed fund and entrepreneurial support programs) and communications.
Excellence in valorization is a critical component of Oncode’s unique approach to building a world-class fundamental oncology research institute. Oncode will become the pivotal partner in the Dutch oncology ecosystem that efficiently integrates fundamental research with translational and clinical research capacity, policy makers, national and international industry, and investors. These outcomes will help attract foreign expertise and investment in fundamental research, clinical development, and the development of new products, services and ventures. It will enable the creation of new or improved screening tools, diagnostics and therapeutic treatments; accelerate the process of validation, commercial development, and adoption; and secure the clinical and economic benefits for the Dutch society.

Figure 1: Valorization channels for translating research into social and economic benefits
Put simply, valorization is the translation of research into social and economic benefits. Research results manifest themselves as intellectual assets in the form of people, scientific publications, know-how, data, research tools, biological materials, software and inventions. Effective valorization supports the translation of intellectual assets via multiple channels for social and economic benefit (see Figure 1). These valorization channels often operate in conjunction with one another in a mutually supportive and synergistic manner.

The immediate beneficiaries of the transfer of these intellectual assets vary by valorization channel and are usually the next link in the innovation chain leading from discovery to implementation. Taking the open access channel as an example, the beneficiaries are other researchers, both academic and industrial, whose research is enabled by free and unfettered access to data, research tools, biological materials, software and publications. In the knowledge transfer channel, the beneficiaries can be practitioners who benefit from new practice guidelines, professionals who benefit from short courses on the use of the latest tools and techniques, or policy makers who benefit from evidence-based research when making policy recommendations. In the technology transfer channel, the initial beneficiaries are startups and existing companies that license technologies to enable their business strategies. The subsequent beneficiaries are the founders and investors who benefit from the support and mentoring provided during the creation and early development stages of their new venture.

Oncode’s valorization objectives are to: accelerate the development of discoveries that result in more effective and affordable cancer treatments; contribute to affordable health care; create value for the Dutch economy; and attract international investment and research funding (see Vision, Mission & Objectives).

The Oncode approach

Oncode is fully mandated by the partner institutions for all valorization activities related to Oncode researchers. This mandate includes the exclusive right to manage intellectual property and negotiate industry-funded research agreements, foster connections with the clinical community and support entrepreneurship – including the creation of new ventures. Oncode will build a critical mass of professionals with deep oncology domain experience and immediate access to support funding and technology transfer tools with the goal of fostering greater impact from our research for the ultimate benefit of patients.

Our philosophy

Oncode believes that knowledge generated from research should be made freely and widely available through publication in peer-reviewed literature. Through our Open Access policy, we seek broad, online public access to our research.

We will adopt approaches that catalyze innovation and create flexible models of collaboration that advance our research and generate knowledge for the benefit of the public. For example, in open models of innovation, which are generally patent free and often rely on quick, straightforward licensing, partners work collaboratively, driving new fields of science and
expanding the knowledge base for all, thereby hastening progress towards the development of medical tools. Collaboration on precompetitive activities can help solve thorny technical challenges, better understand the etiology of disease, validate potential novel medicine targets or identify biomarkers to ascertain if a technology is working. The open model is especially important to lower the hurdles of entry and accelerate the pace of development of health technologies.

Oncode will prioritize societal return over financial return in its patenting and licensing practices. Such practices may include publication, non-exclusive licensing and participation in public sector patent pools, among others. We have no pre-determined preference between for-profit and not-for-profit models and will select the path that provides the best opportunity for the innovation to reach the patient. Sufficient incentives must be in place in these practices to make it attractive for developers to underwrite the cost of bringing a product to market at affordable prices that ensure broad availability.

For example, in addition to more traditional technology transfer models, Oncode will support:

- **open science practices of open data, open access (publications) and open source (software);**
- **knowledge translation projects to inform changes in policy and clinical practice;**
- **non-exclusive licensing of research tools and therapeutic targets;**
- **Global Access Principles to facilitate developing country access to our research; and**
- **the creation of not-for-profit ventures (always with an eye to businesslike operations of the venture that addresses a market fit, financial sustainability and a good management).**

To increase the likelihood that our research results in improved health outcomes, Oncode will seek to involve patients, health practitioners, industry and other stakeholders from the early development of the research concept, through the conduct of the research and the valorization of the research results. Stakeholder involvement will help to inform the research and valorization process through better understanding of the patient, health care provider, insurers and government funders’ needs, challenges and constraints.

**Technology specific approach**

Outstanding research leads to better understanding, perceptive insights and discoveries.

In the course of our research, we will create data; research tools such as organoid lines, animal models and bio-informatics; and develop unique facilities and technical capabilities. We plan to make these quickly and easily available to third parties (academic and industry alike) to enable them to advance their research programs leading to new insights and discoveries.
Discoveries leading to inventions such as software, drug targets and bio-markers will generally be made available through non-exclusive licences enabling as many as possible to benefit while protecting against liability and providing cash flow to support the ongoing costs. In these situations, patents may be used to induce investment required to develop these inventions into practical research tools. In addition, patents may be used as a means to ensure that ongoing access to the invention is maintained and not blocked by third-party improvements. Patent pools may be used to support this objective.

Inventions leading to technologies for screening, diagnostics, medical devices and therapeutics require substantial investment to validate clinical safety and efficacy, to develop methods of production and to obtain regulatory approval. For these technologies, we will seek patent protection to create the financial incentive required for private sector investment. To support this pathway, Oncode has dedicated funds for patenting, technology development, clinical proof-of-concept and seed investment (see The valorization tools). In general, these technologies will be licensed on an exclusive basis with terms including: a termination right in case of non-use (anti-shelving); a royalty scheme that ensures proper return on investment of public funds used to create the relevant IP; ongoing right for Oncode researchers to use the IP for research and scholarly purposes; indemnification obligations and a commitment to Oncode’s Global Access Principles.

Oncode’s intent to develop Global Access Principles follow an international trend towards ensuring developing country at-cost access to products developed from academic inventions. With the dramatic increase of drug pricing in the developed world, these principles will be expanded to include private sector commitment to improving access to health technologies in the developed world. As the understanding of issues relating to societal licensing evolves, balancing ambitious objectives with legitimate business concerns will require patience, determination, and the willingness to be both pragmatic and flexible. Oncode will develop and implement its Global Access Principles during its first year of operations.

**Incentivicing valorization**

Oncode will build a culture in which cooperation in the successful translation of research results has the same prestige as successful fundamental research. Valorization strategies will be integrated into the research program from the beginning, rather than being added afterwards. By evaluating and appraising scientists on their research and valorization performance – and by having valorization performance play a distinctive role in this evaluation – excellence in valorization is then demonstrated and rewarded.

In measuring the success of valorization activities at Oncode, societal impact is a key metric alongside standard throughput, financial and economic measurements.

**Building strong relationships with our researchers**

The valorization team will engage proactively with each of the PIs’ groups to gain an understanding of their research program and expertise, to identify mechanisms to strengthen their research program and to increase translatable opportunities. With this foundational
information in hand, it will actively engage with potential beneficiaries of their work (patients, clinicians) and companies, regardless of size and location, to identify their needs and opportunities for collaboration with Oncode researchers and its research partners. The active flow of information in both directions will foster stronger collaboration opportunities.

The above will include:

- developing an inventory of the research group’s intellectual assets;
- identifying background IP, third party rights, freedom-to-operate, and bundling opportunities (with Oncode IP and third party IP);
- specifying existing and potential partnerships; and
- determining the status of any existing commercialization activities.

Increasingly, success in obtaining research funding requires both scientific excellence and an enabling knowledge translation strategy. The valorization team will work closely with PIs to jointly develop a strategy for their research that promotes a holistic approach in order to activate all of the valorization channels (see figure 1). This brings value to the researchers by enhancing their access to funding, research infrastructure and partnerships and to increased valorization opportunities for their research.

**Building strong relationships with industry**

The valorization business development team will engage with companies and investors throughout the entire research cycle from project development through invention to the translation into the market and clinic.

Examples of related valorization activities include:

- approaching companies to identify their scientific and technical challenges, identifying Oncode researchers and/or facilities that would address those challenges and crafting a collaborative or contract research arrangement;
- facilitating company access to researchers (Oncode and industry) to data, biological materials and specialized expertise;
- facilitating company support (drugs and cash) for investigator initiated clinical trials;
- scouting for business creation opportunities, influencing culture, mentoring founders, and developing company management capacity (entrepreneurs-in-residence);
- supporting new company creation through mentoring, business planning, customer validation, sourcing management, partnering and financing.
Translation to the clinic

Oncode acknowledges the importance of strengthening the connection with the clinic and patients. Fundamental research is part of a long, complex chain directed towards the prevention and treatment of cancer. It is a long way from basic research through translational and clinical research, the development of products and services and bringing them to the market (or to the clinic). Oncode aims to bring basic research and its applications in the clinic closer together.

Patients and clinicians will be involved at the beginning of the research chain to inform scientists about their needs. Oncode will develop a strategy in coordination with the partner institutions, ZonMw and KWF Kankerbestrijding and will take advantage of their experience and networks.

Many of the PIs are located in UMCs with active phase I units and already have a strong track record of working with clinicians in identifying and validating biomarkers as a reliable predictive test for patient selection and treatment outcome. In addition, academic priority programs have been established in which fundamental and clinical research is brought together to facilitate cross-fertilization. Oncode’s scientific theme 5, Identification of critical drug combinations and biomarkers for personalized cancer treatments, builds on this capacity.

Oncode has incorporated €12.5 million in its budget (over five years) for clinical proof-of-concept projects. These funds will be dedicated to preclinical projects, translational projects and clinical studies. This will stimulate collaboration between fundamental, translational and clinical scientists. In the selection of new PIs, we will seek to strengthen our community with MD-PhDs trained in molecular cancer research with an affinity to valorization, and at least two PIs with a focus on translational research.

In order to maintain focus on the translation of fundamental research in products which are benefitting to patients and society, we have embedded a connection to the clinic in the governance structure (see also Organizational Structure and Governance):

- for the Supervisory Board, of the seven members, one member will originate from the patient community;
- a senior clinician-scientist will be appointed on the Research Management Committee;
- a Clinical Advisory Board, with clinicians and a patient representative will advice the Research Management Committee;
- clinicians-in-residence will be part of the valorization support team.
Gathering intellectual assets and leveraging networks

Oncode will bring together the intellectual assets of all the Oncode scientists into a single integrated portfolio. This will promote easier sharing among the scientists, enabling them to better leverage their research through collaboration, common access to infrastructure, reduced duplication, promote adherence to common standards and to secure partnerships with translational and clinical groups that can inform and accelerate their development.

To attain these outcomes, Oncode will:

- provide expertise in clinical and regulatory affairs, health policy and health economics;
- influence policy (where necessary) to overcome regulatory and reimbursement hurdles; and
- source or develop an educational program to enhance the valorization effectiveness of Oncode researchers.

Most importantly, this will become a unique proposition for companies and entrepreneurs in the field who would want to use these intellectual assets to develop new products and services.

Oncode aims to create access to all of the support necessary to valorize the research, but intends to leverage existing programs, infrastructure, funding and talent already available in the oncology ecosystem. We will have funds available to facilitate access, but do not intend to create support systems ourselves if they are already available – locally or internationally.

Contributing to affordable health care

The cost of (Dutch) health care is becoming unsustainable, not in the least by the still rising costs of cancer drugs. As early as 2012, 12 of the 13 newly-approved cancer drugs were priced above $100,000 annually. At NKI-AVL drug costs have more than doubled in the past four years: from €23.8 million in 2013 to €55.7 million in 2016. The problem is widely acknowledged and is the focus of the Ministry of Health’s Vision of Medicines – Bringing New drugs quickly to the patients at reasonable costs.

Working groups, charities and associations such as KWF Kankerbestrijding and the Council for Health Care and Society (RVS) have gathered to better understand the complexity of this issue and explore potential solutions. Common to the reports they produced is the understanding that: 1) the issue is complex; 2) solutions often require international cooperation and collaboration; 3) the entire drug development, certification, manufacturing and distribution system needs to be re-thought; and 4) no single action will address the problem on its own. A concerted and coordinated effort from participants (patients, physicians, hospitals, insurers, government and industry), nationally and internationally, is required. What role can Oncode play?
Oncode believes it can contribute to the reduction of health care costs by: (1) optimizing efficiency of costs during the first stage of drug development (discovery phase); (2) research supporting the rationalized selection of participants in clinical trials; and (3) drug re-discovery to re-purpose abandoned and patent expired drugs.

A troubling element of this problem is the possibility that drugs developed with public funding will subsequently be put on the market at unaffordable prices. While Oncode will have little leverage with its early stage discoveries; the acceleration of new drugs to the clinical proof-of-concept stage and its drug re-discovery program will increase our leverage in negotiating drug affordability provisions with industry.

**Optimizing efficiency**

Oncode will increase efficiency by:

- fostering collaboration between excellent fundamental scientists, working under a common strategy, focusing on a well-defined set of research themes and sharing their data with each other. This will counteract fragmentation and prevent overlap of research activities;

- creating the Netherlands’ first centralized valorization team with domain experience, along with valorization training programs for scientists and the application of metrics assessing the research groups contribution to valorization. This will considerably enlarge the number of discoveries becoming transferred into practical applications to the benefit of patients.

**Rationalized selection of clinical trial participants**

- supporting the rationalization of the selection of participants in clinical trials by:
  - applying scientific argumentation based on the understanding of the mechanisms of cancer (which patients are likely to benefit from this drug?);
  - developing and applying clinically useful biomarkers that enable to segregate patient populations into likely responders and unlikely or non-responders, or that can determine start-stop criteria for drug treatments (surrogate endpoints), thus limiting unnecessary use of medication.

- these methods will allow for fewer and smaller trials as opposed to the big expensive and often inefficient trials, which are usually carried out;

- use of new tools, such as organoids, that provide alternative approaches to selecting effective therapeutic agents for individual patients (personalized medicine);

- the use of proof of concept clinical trials, funded through Oncode, in small selected patient cohorts to demonstrate clinical utility of the designed therapy.
Drug re-discovery

In addition to Oncode’s fundamental oncology research program, we will establish a program of drug re-discovery, where we conduct research to re-purpose abandoned and patent-expired or expiring drugs. This includes:

- investigating which drugs, developed for one cancer indication, can be used to treat other types of cancer;

- focusing on drugs that have lost or will soon lose patent protection and search for novel applications for these off-patent drugs;

- for drugs stopped in clinical development due to lack of single agent activity, systematically searching for combinations with other drugs based on insight into reaction mechanisms.

This program is centred on developing a better understanding of the mechanisms of action at the molecular level and using this understanding to apply rationalized selection of trial participants, supported by biomarkers and new tools (organoids), in clinical proof of concept trials in small selected patient cohorts.

Since drug re-discovery focused on drugs already approved for use in the clinic, it circumvents the need for the lengthy and expensive pre-clinical development and phase I (safety) clinical trials. Given that these drugs have a strong mechanistic rationale and an associated biomarker of response (key aspects of our efforts), the new registration trials can be smaller and the success rate can be higher than in traditional clinical trials.

Oncode believes that by working with this particular class of drugs (off patent, previously failed) to re-ignite their development, we are in a better negotiation position with industry to deal with issues of transparency, data exclusivity and pricing (both in absolute and volume related terms). Patents will be filed, where possible, to secure our intellectual property position. In negotiations

![Figure 2: Oncode’s fundamental research and drug re-discovery programs](image_url)
with industry, we will explore price caps, as a return on the investment by the Dutch society, as well as price-volume clauses (for instance, in case a one-agent drug turns out to be applicable for other indications). At a minimum, a most favored nation’s provision should be part of the agreement negotiations: the price charged in the Netherlands should not be higher than the price charged in any other EU-country.

For those drugs that are not financially attractive to industry, Oncode will work with new players, including generic drug makers, social investors, academic drug development centers and the Fair Medicine initiative. We strongly advocate the Fair Medicine coalition approach and have started discussions on collaboration with them. Fair Medicine and Oncode agreed to enter into a Memorandum of Understanding to formalize their intent to work together. In addition to candidates resulting from our drug re-discovery program, our patent fund, clinical proof-of-concept fund and oncology seed investment fund will position us to be an active partner. Collectively, we will set the conditions for agreements based on a partnership which focuses on common interests such as the affordability of drugs that we develop.

**Reporting**

Since affordability of health care is such a pressing problem, Oncode will have semi-annual meetings with government experts to discuss its affordable health care strategy and active projects. We will include impact statements on the affordable health care pilots and the development of the strategy on affordable health care in our annual report. We will actively share our progress, successes and failures, to enable others to learn from our efforts and in that way, fulfill our pioneering role within this field.
The valorization tools

<table>
<thead>
<tr>
<th>Valorization Support of Fundamental Research</th>
<th>Research Outputs</th>
<th>Translational Activities</th>
<th>Valorization Outputs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Development</strong></td>
<td><strong>Performance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Stakeholder engagement</td>
<td>• Access to research materials, tools and data</td>
<td>• Technology development</td>
<td>Open Science</td>
</tr>
<tr>
<td>• Identify and recruit partners</td>
<td>• Financial management support</td>
<td>• Pre-clinical development</td>
<td>HQP</td>
</tr>
<tr>
<td>• Secure access to research tools and data sets</td>
<td>• Contract management</td>
<td>• Clinical validation</td>
<td>KT Projects</td>
</tr>
<tr>
<td>• IP landscape assessment</td>
<td>• Stakeholder relations</td>
<td>• IP management</td>
<td>Licenses</td>
</tr>
<tr>
<td>• Knowledge mobilization strategy</td>
<td>• Intellectual Property management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Grant applications</td>
<td>• Research training and mentoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Contract negotiations</td>
<td>• Inventions</td>
<td></td>
<td>Start-ups</td>
</tr>
</tbody>
</table>

Oncode will have the tools and financial means necessary for superior valorization. This includes budget for subscriptions to intelligence databases, interns bringing complementary skills to projects and international travel for business development. In addition, it will manage three funds:

**IP fund**

**Description:** €500 thousand per year for the assessment, strategy development, filing, prosecution and management of Oncode technologies. This fund will be under the control of the business development and IP management members of the valorization team.

**Investments:** The IP fund will be used to file and prosecute provisional and PCT (Patent Cooperation Treaty) patents through to the entry of the national phase. The costs per patent are estimated at €7 thousand for a provisional filing, €15 thousand for a PCT filing and €10 thousand to prosecute the PCT filing. The costs are spread over 30 months as an application moves from provisional filing, to PCT filing, to the entry into the national phase.

**Criteria:** The go/no criteria for pursuing patent protection varies by the stage of filing.

- **provision filing (t=0 months): preliminary business assessment and review of prior art conducted by valorization team;**
• PCT filing (t=12 months): in-depth assessment examining patentability, freedom-to-operate, IP strategy, business opportunity, technical feasibility and competitive landscape;

• PCT prosecution (t<30 months): continuation of assessment augmented with additional information from technology development and/or clinical proof-of-concept projects.

• National phase (t>30 months): on an exceptional basis for truly outstanding opportunities.

Technology development fund

Description: Fundamental science often yields inventions that are underdeveloped and often many years away from the market. They may be based on a single observation and need additional time and effort to confirm their validity, broaden their application or demonstrate that they are viable outside of a lab setting. The technology development fund, set at €1 million per year, provides the critical capital to de-risk these technologies and increase the likelihood of successfully licensing. Examples of project supported with these funds include:

• proof-of-concept, prototype development and scale-up;

• generation of data to confirm and expand patent claims;

• third party market research.

Investments: Individual projects will range in value from €10 thousand to €150 thousand and will operate on an open call basis. For larger projects, external funds will be used to cost-share and augment project funding (i.e. Swanbridge Capital, ERC proof-of-concept)

Criteria: Funding criteria will be developed based on the A.C.E Evaluation, which includes:

• (A)ffirmations: Three questions that get to the root of the three evaluatory thrusts of technology assessment, commercial assessment, and project planning. Three positive responses move a project forward to further investigation (C);

• (C)riteria: Nine areas of consideration related to the thrust areas;

• (E)xtra considerations: Special factors to consider use of funds.

One exception to this market driven assessment, would be for those technologies with a potential for a direct clinical impact by no clear route to commercialization.

**Oncology seed investment fund**

**Description:** Targeted at early stage business opportunities serving needs in the oncology sector, this fund is intended to provide the necessary capital to advance a business opportunity from pre-incorporation through incorporation to the stage where the venture can attract direct investment and/or sales revenue.

**Capitalization:** Investable funds are capitalized through a Future Fund loan (90% of funds) and KWF (10%) of funds. Fund operational costs including staffing, operations and clinical proof-of-concept, which are provided by Oncode.

**Fund term:** 15 years with initial and follow-on investing concentrated during years 1-10. During the term, proceeds from liquidity events are reinvested in the fund.

**Investment philosophy:** Unlike traditional investment funds, the investment philosophy is based on enabling companies to transition from concept to viable businesses that fulfills a market need in the oncology sector. This includes service-based ventures, technology companies and screening, diagnostic and therapeutic focused ventures. Companies with products that service an orphan indication with little chance of a substantial finance return, but which present a viable plan to service this limited market, will also be eligible for investment. Particularly for ventures resulting from our drug re-discovery program, direct investment from this fund will increase our leverage in determining the development path for the drug candidate and directly address the issue of affordability of drugs developed. Investments are available for both for-profit and not-for-profit ventures.

The goal of the oncology seed investment fund is to transform research ideas into market ready investment opportunities with competent management in place:

- **early stage investments will be accompanied by intensive mentoring, professional intellectual property management, pre-investment technology de-risking and where possible, preliminary clinical validation;**

- **focus on building viable companies rather than investing for maximum financial return. There is no pre-set filter for the size of the market opportunity or minimum investment returns.**

**Nature of investments:** Investments may be made in the form of loans, convertible debentures, common shares, preferred shares, options and warrants. Loans will be the preferred investment vehicle for ventures with near term revenue potential (IT and service based ventures). Interest will be charged at commercial rates with payback over two to five years. Convertible debentures will be used for pre-seed and seed investments to defer valuation discussions. Convertible debentures will carry a commercial interest rate and the conversion to equity will include a premium (20%-35%).

Total investment in a single entity may not exceed €1 million or 20% of the total funds under management.
Co-investment will be required. Sources of co-investment will vary with the investment stage and includes angels and foundations in early stages and venture capital in the later stages. Non-dilutive financing through government granting programs and tax incentives will also be exploited.

**Fund operation:**

- *the oncology investment fund operates as a division within Oncode reporting to the Managing Board;*

- *fund management will be provided by a dedicated fund manager with the responsibility to conduct due diligence on investment opportunities, negotiate investments from term sheet to closing documents, source co-investment partners, monitor investee performance and manage the investment portfolio;*

- *entrepreneurs-in-residence will be used to mentor founders, develop financing strategies, source management and board talent and groom companies for investment;*

- *all investments must be approved by the Managing Board subject to the recommendation of an independent investment committee consisting of individuals with early stage investment experience representing both investors and company perspectives.*
Valorization results

The results from Oncode’s valorization efforts will present differently with the passage of time. In the near term (1-3 years), we expect to see changes in the researcher’s attitudes towards integration of stakeholder engagement and valorization as an integral part of their research program. There will be an increase in research productivity as our researchers achieve greater efficiency from reduction in duplication, access to common standards, common research infrastructure and international research partnerships. There will be a maturing of the valorization ecosystem with partnerships, networks and relationships forming amongst the various individuals and organizations: researchers, clinicians, industry, entrepreneurs, professionals and investors.

At the request of other institutes, the valorization team will provide advice and services to academic and technology transfer teams across the Netherlands. In addition, KWF Kankerbestrijding and Oncode intend to set up a close collaboration for valorization activities.

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Total</th>
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<tbody>
<tr>
<td><strong>Research Personnel</strong></td>
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<td>829</td>
<td>843</td>
<td>862</td>
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<td>€91,016</td>
<td>€92,516</td>
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<td>- Invention Disclosures</td>
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<td>- New Patent Filings</td>
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<td>- Options / Licenses Executed</td>
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<td>- Spin-off Companies</td>
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<td>- Affiliated Start-ups</td>
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<td>3</td>
<td>3</td>
<td>3</td>
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</table>

Table 4: Projected level of Oncode Phase I intellectual property activity (amounts € x 1,000). These projections are based on an analysis of the performance of American research hospitals and universities as reported in the Association of University Technology Managers FY2014 survey.

Based on the projected growth of the Oncode research enterprise in terms of research personnel and research funding to PIs, the projected level of intellectual property is shown in Table 4: projected level of Oncode Phase 1 intellectual property activity.

In the medium term (5-7 years), Oncode will be able to harvest the benefits of building this valorization ecosystem as demonstrated not only by an increased number of transactions, but also by the increased quality of the intellectual assets (i.e. IP with clear title, freedom-to-operate, packaged with ancillary tools, data, and know-how). This will enable the accelerated development of the intellectual assets along the innovation pathway. Oncode technologies will be licensed and in early stage development in the clinic. New companies will be created and in the early stages of financing and product development. International research partnerships will be actively bringing a broad range of research, technology and market opportunity to the Netherlands. These outcomes will help attract international expertise and investment in
fundamental research, clinical development, and the development of new products, services and ventures.

In the longer term (7+ years), we will start to see the emergence of new products, services and policies, with attendant benefits accruing to patients, investors, the health care system and Dutch society.
Organizational Structure and Governance

Oncode – a virtual research institute

**Funders**
- KWF Kankerbestrijding
- Ministry of Health, Welfare and Sport
- Ministry of Education, Culture and Science
- Ministry of Economic Affairs
- Topsector Life Sciences and Health
- Partner Institutions

**Partner Institutions**
- NKI
- Hubrecht Institute
- UMC Utrecht
- Erasmus MC
- LUMC
- AMC
- Radboudumc
- Radboud University
- Princess Máxima Center

**Oncode Institute**

43 Research Groups
>560 Researchers

Oncode will operate in a virtual manner: a central staff of 20-25 will provide general management and valorization services to its network of over 560 researchers across nine research institutions, but it will not have its own research facilities or own research staff. All the associated researchers will be employed by one of the partner institutions, at which the actual research will be conducted.

**Legal entity**

Oncode will be established as a foundation, which is the most appropriate type of legal entity given its goals as an independent not-for-profit organization and its funding arrangements. As its activities expand, additional legal entities may be established under the auspices of the foundation.

**Good governance**

To ensure good governance, Oncode will develop a good governance charter based on the rules in the Dutch Corporate Governance Code, including regulations applying to the Supervisory Board, the Managing board, the advisory boards and committees and policies related to conflict-of-interest and scientific integrity. The good governance charter is to be approved by the Oncode Supervisory Board.
Relationship with principal partners

Contribution agreements

During the first five years, most of the financial support for OncoCode will be provided by a coalition of public and private sector funding sources: KWF Kankerbestrijding, the three Dutch Ministries (Health Welfare and Sport; Education, Culture and Science; Economic Affairs), Topsector Life Sciences & Health and the partner institutions.

The relationship between OncoCode and the funders (not being partner institutions) will be set out in bilateral contribution agreements. The funders have agreed to common reporting and communications requirements, integrated representation on the OncoCode Supervisory Board, key performance indicators and an evaluation process. The bilateral agreements will allow the specific needs of individual funders, such as additional information to support the funder's internal and public accountability requirements, to be addressed.

In addition to the formal reporting requirements, OncoCode will convene a group meeting of all funders twice per year to review activities, address challenges and identify opportunities. One of the meetings will coincide with the OncoCode annual scientific meeting.

Research staff & affiliation

At the outset, 43 PIs from various research institutions have agreed to join OncoCode. These PIs and their research teams (postdocs, PhDs, technicians and support staff) will continue to work at their existing research institutes (the partner institutions). During the first two years, OncoCode will support the partner institutions in their worldwide recruitment of additional PIs to supplement and enhance its research capacity. In all cases, researchers will be employed by a partner institution and subject to the policies, procedures and collective agreements of that institution.

Affiliation agreements, based on a common template, will be made between OncoCode and each partner institution setting out the expectations, rights and responsibilities of each party. Intellectual property arrangements are an important part of the affiliation agreements.

Intellectual property

The partner institutions grant OncoCode the exclusive right to manage intellectual property, including the right to manage patent prosecution and to develop, market and license the intellectual property. The institutions shall retain the right to use the intellectual property for scholarly and clinical purposes. OncoCode will bear all of the costs of managing the intellectual property and shall have the right to recover a 10% management fee plus its out-of-pocket legal costs from licensing revenue. The remainder is divided between the partner institutions responsible for creating the licensed intellectual property in proportion to inventorship. The partner institutions shall channel at least 70% of the IP revenues to oncology research. While each institution has its own internal distribution formula, on average inventors receive 25% of
net revenues with the remaining 75% distributed among the research group, the central administration, the technology transfer office and the academic department (see Licensing and Investment Revenues).

The Oncode valorization team will be independent from the TTOs of the host institutions, but it will work closely with them. It will report regularly to the TTO on the valorization status of the partner institution’s intellectual property, under its management. In the event that Oncode decides not to actively valorize the partner institution’s intellectual property, it will arrange for the timely return to the partner institution.

This intellectual property arrangement is not absolute. All parties have agreed to work creatively and collaboratively to manage the myriad of different situations that will arise related to existing third party relationships, background intellectual property rights and legacy issues. In this regard, we will be guided by the principles of maintaining existing relationships (especially with scientific collaborators), ensuring that the integrity of the intellectual property is not jeopardized and that its impact is enhanced.

**External research funding**

Oncode will assume responsibility for providing business development and supporting grant development for projects related to Oncode’s PIs and it will review (negotiate) IP related terms on all external funded projects. Furthermore, Oncode may act as the coordinating party for EU grants. Oncode is the contracting partner for projects with industry. Funding from the Dutch government, grants and foundations will continue to flow directly to the partner institutions.

**Publication and publicity**

Every publication by an Oncode scientist will specify the affiliation with Oncode Institute and the relevant partner institution, thus providing visibility for both organizations. We will provide an affiliation-format for the scientists. In its promotional material and media communications Oncode will acknowledge the participation of its partner institutions and principal funders.
Organizational structure

The Supervisory Board will supervise the Managing Board, the implementation of Oncode’s strategy and the general course of affairs related to that strategy. The Supervisory Board provides the Managing Board with advice, requested or not requested.

The supervision of the Managing Board by the Supervisory Board includes:

(1) achievement of Oncode’s objectives; (2) Oncode’s strategy; (3) internal risk management; (4) financial reporting process; (5) compliance with legislation and regulations, including funding agreements; (6) relation with Oncode’s stakeholders; (7) social responsibility issues that are relevant to Oncode or any of its stakeholders; and (8) the selection process of the PIs.
The Supervisory Board will consist of seven members:

- **an independent chair**
- **nominees (4), each of the following stakeholders has the right to nominate a person to be appointed on one position:**
  - KWF Kankerbestrijding
  - Dutch government (Ministry of Economic Affairs, Ministry of Health, Welfare and Sport and the Ministry of Education, Culture and Science)
  - affiliated research institutes, not being UMCs
  - affiliated UMCs
- **others (2), originating from:**
  - business community
  - patients community

The Supervisory Board acts in accordance with the interests of Oncode, taking the interests of Oncode’s stakeholders into account. Though several members of the Supervisory Board will be appointed on nomination or recommendation of stakeholders, they shall perform their duties independently, in the best interests of Oncode as a whole. The responsibility for the proper performance of their duties is vested collectively in the Supervisory Board.

The composition of the Supervisory Board should reflect a variety of experience, age, cultural background and nationality and gender. The specific knowledge and experience to be combined in the Supervisory Board are:


The initial members of the Supervisory Board will be appointed for a term of two to four years. In order to create staggered board renewal, starting in year three, 25% of the original members will be replaced each year by new members. This means that the Supervisory Board will be completely renewed after six years. The choice for the initial two-year period is based on the assumption that skills and experiences to be required of Supervisory Board members may be different in case of a starting enterprise than when a more consolidated situation has been established.
Managing Board

The Managing Board will consist of the General Director, the Valorization Director and the Chief Scientific Officer.

The Managing Board is responsible for:

1. achievement of Oncode’s objectives;
2. creation and execution of the strategy (including the scientific strategy and the valorization strategy);
3. coordination of assessment procedures and monitoring results;
4. decisions on affiliations with PIs and their research groups or concluding such affiliations (both after consultation of the Research Management Committee);
5. internal risk management;
6. financing;
7. compliance with legislation and regulations, including funding agreements;
8. relations with stakeholders; and
9. social responsibility issues that are relevant to Oncode.

General Director

The General Director will be appointed as chair. The chair has no hierarchic authority over the Valorization Director and the Chief Scientific Officer, but is charged with some specific responsibilities:

- in coordination with the Valorization Director and the Chief Scientific Officer, he/she is responsible for policy-making in general and the development and implementation of Oncode’s strategy in particular;
- shaping and implementing the execution of Oncode’s mission in the fields of science policy and culture, people and development, communication and collaboration, finance and operations;
- leading the general support team (see below);
- maintaining effective relations with Oncode’s funders, partner institutions and other stakeholders, resulting in securing Oncode’s continuation after phase 1.

Valorization Director

The Valorization Director develops and leads an effective translation/transfer process to ensure that Oncode research results will achieve their maximum clinical and economic potential. The Valorization Director is responsible for:

- developing a valorization program that identifies clinical and commercialization opportunities emerging from Oncode research and enables maximum valorization impact;
• facilitating engagement between relevant clinical and industrial partners and Oncode researchers with the goal of identifying joint research projects, intellectual property activities with a view to licensing and entrepreneurial opportunities;

• leading the valorization team (see below).

The Valorization Advisory Board (see below) reports to the Valorization Director.

**Chief Scientific Officer**

The Chief Scientific Officer provides scientific leadership and facilitates the most effective research environment for Oncode. This part-time position (approximately 0.2 FTE) has the following responsibilities:

• as Oncode’s scientific leader, the Chief Scientific Officer interfaces with researchers, partner institutions, funders and other stakeholders on research related issues;

• through his role as the chair of the Research Management Committee, the Chief Scientific Officer facilitates the establishment of the scientific priorities for (support of) Oncode;

• promoting Oncode’s research related objectives and activities to the research community and private and public sector organizations.

The founding Chief Scientific Officer will be appointed for one year. The Supervisory Board will establish the selection procedure for future Chief Scientific Officers after Oncode has been founded. The Chief Scientific Officer position will be filled by one of the members of the Research Management Committee on a rotating basis.

**Research Management Committee**

The Research Management Committee provides guidance and policy advice to the Managing Board on research related themes, including: the selection of PIs, development of the scientific strategy and annual plans, coordination of scientific monitoring and reporting and appropriation of funds. In addition, the Research Management Committee will interface with each of the research themes to assess ongoing plans and needs, identify growth strategies and facilitate inter-theme collaboration.

The Managing Board will consult the Committee on research related topics and decides upon these topics by recommendation of the Research Management Committee. As a rule, the Managing Board does not decide on scientific/research related topics if these are not discussed with the Research Management Committee.

The Research Management Committee will initially consist of the five founding scientists (including the Chief Scientific Officer) and a senior clinician-scientist. The Chief Scientific
Officer is the chair of the Committee. The General Director and the Valorization Director will attend the Research Management Committee meetings.

Early in phase I (2017-2022), Oncode will develop a succession plan for the founding scientists in the Research Management Committee, paving the way for younger scientists to take an active role in the management of Oncode. The first change in the Research Management Committee is anticipated at 18 months after the incorporation of Oncode.

**Executive Committee**

The General Director and the Valorization Director together with the Chief Financial Officer and the People & Development Manager, will form the Executive Team, which will be responsible for strategy, planning, financing, day-to-day operations and stakeholder relations. The Chief Scientific Officer will be involved in the Executive Committee concerning research related themes.

**International Advisory Board**

A committee composed of seven independent experts from abroad will form the International Advisory Board to advise on issues intrinsic to Oncode. These individuals will be internationally recognized for their expertise and have no conflicts of interest with Oncode, its funders or the partner institutions. As a whole, the International Advisory Board will combine expertise in molecular oncology, technology transfer and cancer care. The International Advisory Board will meet annually to advise upon Oncode’s strategy on an institutional and on a PI level. An International Review Committee will assess Oncode’s performance in the mid-term assessment (See Assessment and Monitoring Processes).

**Clinical Advisory Board**

In the Clinical Advisory Board, clinicians and patient representatives will provide advice on Oncode’s strategy, the operation of programs (i.e. clinical proof-of-concept) designed to promote translational and clinical connections and opportunities to enhance individual projects. It provides advice to Oncode researchers on translational and clinical issues related to their research. It will advise on all applications for funding from the clinical proof-of-concept fund.

The Clinical Advisory Board will consist of five to seven oncology clinicians, clinician-scientists and a patient representative. The clinician-scientist on the Research Management Committee will be appointed as the chair of the Clinical Advisory Board. The Clinical Advisory Board will be reporting to the Research Management Committee.
Valorization Advisory Board

Reporting to the Valorization Director, the Valorization Advisory Board will bring together approximately seven individuals with experience in the identification, development, clinical validation, regulatory approval, commercialization and financing of oncology technologies from the patient, industry and investment communities. It will meet regularly with key members of the valorization team, inventors, clinicians-in-residence and entrepreneurs-in-residence in order to review inventions under management and to advise on development plans, intellectual property issues, critical uncertainties, potential partners and commercialization opportunities. The Valorization Advisory Board will also provide the Managing Board with advice on societal matters, such as affordable health care.

Investment Committee

Reporting to the Managing Board, the Investment Committee will consist of three to five individuals with early stage investment experience representing both investor and company perspectives. The role of the Investment Committee is to recommend all investments made from the seed fund. This committee will be able to draw upon the broader experience of the Valorization Advisory Board and external advisors as required.

The general support team

The general support team supports the realization of Oncode’s mission in the fields of science policy & culture, people & development, communications & collaboration and finance & operations. The team of approximately 10 FTEs supports the General Director and the Chief Scientific Officer and reports to the General Director. The team works closely together with the partner institutions and scientists.

The staffing, set out below, is based on the anticipated needs of the Institute when fully operational (anticipated for 2018). This will adapt to the Institute’s needs over time.

Science policy & culture

Oncode aims to provide exceptional resources, helping accomplished scientists and top talent come together under the best possible circumstances. The science policy & culture team will facilitate integrating science, collaboration, education and operational efforts. The team will focus on a broad spectrum of science-related themes, including:

- shaping, implementing and fostering Oncode’s innovation culture, in collaboration with people & development (see below);
- developing and executing on the reporting and assessment structure for Oncode PIs;
- shaping and developing the training and coaching programs, in collaboration with the people & development team (see below);
• enabling open science (including open access and FAIR data principles);
• identifying and pursuing international funding opportunities; and
• stakeholder management.

People & development

The people & development team is responsible for:

• leading Oncode’s HR management, including strategy, talent management, procedures, employment contracts etc.;
• recruiting Oncode staff and supporting the partner institutions on recruiting new researchers;
• shaping, implementing and fostering Oncode innovation culture, in collaboration with the science policy & culture team; and
• Oncode as a learning institution: shaping, implementing and improving the training and coaching programs, in collaboration with the science policy & culture team.

Communications & collaboration

Our communications team facilitates the sharing of new insights and developments with donors, funders and the scientific community. The team is furthermore responsible for the shaping, development and operations of the digital platform for collaboration and debate.

The team oversees communications and public relations for the Institute, including communications strategy, media relations, advancing the public understanding of science, internal communications and science events. Furthermore, it drives and guides building the virtual institute inside the organization itself and is responsible for web presence and creative content.

Finance & operations

The Chief Financial Officer (CFO) & Treasurer oversees budget and financial analysis, the controller’s office, treasury, internal audit, tracking of funding and procurement. Finance officers will support the CFO. The operations team (including IT) reports to the CFO.

The operations team will be charged with advancing operational success across the organization. Tasks include: overseeing key operational functions, including administrative services, and responsibility for facility management.

IT supports all information technology areas of the Institute including computer infrastructure, applications, telecommunications, audio visual and desktop support services.
The valorization support team

The valorization support team will consist of a staff of approximately ten and will be guided by the Valorization Advisory Board. Team members will contribute their expertise in business development, new company creation, intellectual property, large public funding programs, international collaborative research, knowledge transfer and communications. To supplement the team’s direct skills in areas such as law, taxation and regulatory affairs, Oncode will draw from a cadre of external experts to bring in unique expertise, as required. Strong interpersonal and communications skills, demonstrated networking capabilities, the ability to build effective relationships, creativity, persistence and a clear understanding of the academic, clinical and business environments will be essential to success.

The valorization support team will be led by the Valorization Director and consists of the following members:

Business development associates

Senior and junior positions are the front line staff with responsibility for scouting, developing, marketing and valorizing opportunities resulting in:

- increased research funding from industry, granting agencies and foundations;
- technology licensing;
- knowledge translation projects; and
- new ventures.

These professionals will possess a PhD (life sciences) and have extensive industry experience.

Intellectual property managers

The IP managers are responsible for assessing IP positions, developing IP strategies and securing IP protection for the Oncode research community. These positions will be staffed by patent agents and/or lawyers.

Contract administration managers

The contract administration managers are responsible for all aspects of contract negotiation and administration with third parties and partner institutions related to funded research projects, material transfers and non-disclosure agreements.

Clinicians-in-residence

These one day-per-week positions will circulate among the research groups to increase the understanding of clinical realities, identify and shepherd clinical development opportunities,
and facilitate networking between PIs and the clinical community. These individuals will come from the clinical community and will have access to the Oncode clinical proof-of-concept fund to facilitate development projects.

**Entrepreneurs-in-residence**

These one day-per-week positions will circulate among the research groups to increase the understanding of company creation realities. They will identify individuals (PhDs, postdocs, PIs and technicians) who have an interest in company creation and will assist them in moving through the ideation, customer validation (and possibly clinical validation) and into the pre-incorporation phase. These individuals will be seasoned entrepreneurs who have seen companies through from concept to successful exits. They will have access to the Oncode seed investment fund as well as an extensive network of investors and business professionals.

**Investment manager**

This position is responsible for managing the seed investment fund including conducting due diligence, negotiating investment terms and agreements, syndicating investments, monitoring investee performance and managing the investment portfolio. This individual will work closely with the entrepreneurs-in-residence and the Investment Committee to qualify investment opportunities.
Financial Plan

Phase I (2017-2021) highlights
(all amounts € x 1,000)

<table>
<thead>
<tr>
<th>REVENUES</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding Partner Investments</td>
<td>€ 22,791</td>
<td>€ 23,501</td>
<td>€ 24,121</td>
<td>€ 24,071</td>
<td>€ 24,271</td>
<td>€ 118,755</td>
<td>82.6%</td>
</tr>
<tr>
<td>External R&amp;D Funding</td>
<td>€ 1,000</td>
<td>€ 2,500</td>
<td>€ 4,000</td>
<td>€ 6,000</td>
<td>€ 6,500</td>
<td>€ 20,000</td>
<td>13.9%</td>
</tr>
<tr>
<td>Fee-for-Service</td>
<td>€ 120</td>
<td>€ 320</td>
<td>€ 320</td>
<td>€ 320</td>
<td>€ 320</td>
<td>€ 1,400</td>
<td>1.0%</td>
</tr>
<tr>
<td>Licensing and Investments</td>
<td>€ 0</td>
<td>€ 309</td>
<td>€ 679</td>
<td>€ 1,070</td>
<td>€ 1,551</td>
<td>€ 3,610</td>
<td>2.5%</td>
</tr>
<tr>
<td>Total</td>
<td>€ 23,911</td>
<td>€ 26,630</td>
<td>€ 29,120</td>
<td>€ 31,461</td>
<td>€ 32,642</td>
<td>€ 143,764</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 4: Oncode Phase I Revenue Forecast

Oncode Revenues are derived from four principal sources:

1. Funding Partner Investments (KWF Kankerbestrijding; Ministry of Economic Affairs (EZ); Topsector Life Sciences & Health; Ministry of Health, Welfare and Sport (VWS); Ministry of Education, Culture and Science (OCW); the partner institutions);
2. R&D Funding from industry and international granting bodies;
3. Fee-for-service arrangements with research institutions; and
4. Licensing and investment revenue.

During Phase I (2017-2021), the total revenue is forecast to increase from €23,911 (year 1: 2017/19) to €32,642 (year 5: 2021/22). The annual proportion of funding provided by the Funding Partners decreases from 95% (Year 1) to 74% (Year 5).

<table>
<thead>
<tr>
<th>EXPENSES</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management &amp; Admin</td>
<td>€ 1,382</td>
<td>€ 1,298</td>
<td>€ 1,478</td>
<td>€ 1,595</td>
<td>€ 1,709</td>
<td>€ 7,461</td>
<td>5.2%</td>
</tr>
<tr>
<td>Pre-incorporation Expenses</td>
<td>€ 1,520</td>
<td>€ 0</td>
<td>€ 0</td>
<td>€ 0</td>
<td>€ 0</td>
<td>€ 1,520</td>
<td>1.1%</td>
</tr>
<tr>
<td>Research Support Total</td>
<td>€ 18,490</td>
<td>€ 21,450</td>
<td>€ 22,860</td>
<td>€ 24,740</td>
<td>€ 25,210</td>
<td>€ 112,750</td>
<td>78.6%</td>
</tr>
<tr>
<td>Valorization Total</td>
<td>€ 2,288</td>
<td>€ 3,835</td>
<td>€ 4,747</td>
<td>€ 5,114</td>
<td>€ 5,680</td>
<td>€ 21,664</td>
<td>15.1%</td>
</tr>
<tr>
<td>Total</td>
<td>€ 23,680</td>
<td>€ 26,583</td>
<td>€ 29,084</td>
<td>€ 31,449</td>
<td>€ 32,599</td>
<td>€ 143,395</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 5: Oncode Phase I Expense Forecast

Total expenses are forecast to increase from €23,760 (Year 1) to €32,599 (Year 5). The expenses are forecast to be made in the following proportion:

- **Research** €112,750 (78.6%)
- **Valorization** €21,664 (15.1%)
- **Management and Administration** €7,461 (5.2%)
- **Pre-incorporation costs** €1,520 (1.1%)
For the period, total research expenditures are forecast to be €112,750 of which:

- **Base Research Support** €63,950 (56.7%)
- **Targeted Research Programs** €30,000 (26.6%)
- **External Research Funding** €18,800 (16.7%)

**Risks**

- Funding is based on one five-year term with renewal based on pre-determined criteria. Continuation of government programs (TKI, Translational Research Program) are not guaranteed;
- Reduced industry funding impacts the associated TKI allowance (€500 over phase I);
- Industry and international funding are estimates but have a neutral impact considering revenues/expenses; and
- It is assumed that the 21% Value Added Tax (VAT) will not apply to transfer of research funds or licensing revenue. An advance tax ruling will be sought from the Dutch Tax Authority.

**Financial controls**

The five-year pro forma budget is prepared for the purpose of securing funding. Annually, a one-year budget and three-year forecast will be submitted to the Supervisory Board for approval. The following financial reports are required:

1. budget-to-actual reports submitted quarterly to the Supervisory Board;
2. annual financial reports (audited) submitted to Supervisory Board and funding partners;
3. specific reports for future fund, TKI allowance, intellectual property and externally funded research projects; and
4. financial reporting required from partner institutions for research funding (Oncode and external funding).

A policy framework will be established to govern travel expenses, entertainment, eligible R&D expenses.

**Investment portfolio**

Under the valorization program, Oncode will manage an internal investment fund with up to €1,000 per year available for early stage investments. During phase I: we forecast investing a total of €3,410 in fifteen companies. Most investments will be through convertible debentures with four estimated as equity investments. Investments will be approved by an independent investment committee and managed by a professional investment manager.
## Table 6: Oncode Phase I Revenue and Expense Projections

<table>
<thead>
<tr>
<th>Notes</th>
<th>REVENUES (all amounts in € x 1,000)</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Funding Partner Investments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>KWF Kankerbestrijding</td>
<td>€12,740</td>
<td>€12,740</td>
<td>€12,740</td>
<td>€12,740</td>
<td>€12,740</td>
<td>€63,698</td>
<td>44.3%</td>
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<tr>
<td>2</td>
<td>Min of Economic Affairs (EZ)</td>
<td>€1,250</td>
<td>€1,850</td>
<td>€2,450</td>
<td>€2,400</td>
<td>€2,600</td>
<td>€10,550</td>
<td>7.3%</td>
</tr>
<tr>
<td>3</td>
<td>Top Sector Life Sciences</td>
<td>€3,125</td>
<td>€3,125</td>
<td>€3,125</td>
<td>€3,125</td>
<td>€3,125</td>
<td>€15,625</td>
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<tr>
<td></td>
<td>TKI Allowance - KWF Contribution</td>
<td>€0</td>
<td>€110</td>
<td>€130</td>
<td>€130</td>
<td>€130</td>
<td>€500</td>
<td>0.3%</td>
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<tr>
<td></td>
<td>TKI Allowance - Industry R&amp;D</td>
<td>€0</td>
<td>€240</td>
<td>€240</td>
<td>€240</td>
<td>€240</td>
<td>€1,200</td>
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<tr>
<td>4</td>
<td>Min of Education (OCW)</td>
<td>€2,239</td>
<td>€2,239</td>
<td>€2,239</td>
<td>€2,239</td>
<td>€11,195</td>
<td>7.8%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Min of Health (VWS)</td>
<td>€2,000</td>
<td>€2,000</td>
<td>€2,000</td>
<td>€2,000</td>
<td>€2,000</td>
<td>€10,000</td>
<td>7.0%</td>
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<tr>
<td>6</td>
<td>ZonMW - Translation Research</td>
<td>€239</td>
<td>€239</td>
<td>€239</td>
<td>€239</td>
<td>€1,195</td>
<td>0.8%</td>
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<tr>
<td>7</td>
<td>Partner Institutions</td>
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<td>€958</td>
<td>€958</td>
<td>€958</td>
<td>€4,792</td>
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<td>Funding Partner Investments</td>
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<td>€23,501</td>
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</tr>
<tr>
<td>8</td>
<td>External R&amp;D Funding</td>
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<td></td>
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<tr>
<td>9</td>
<td>Fee for Service</td>
<td>€120</td>
<td>€120</td>
<td>€120</td>
<td>€120</td>
<td>€120</td>
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<td></td>
<td>Princess Maxima</td>
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<td>10</td>
<td>Intellectual Property</td>
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<td>11</td>
<td>IP Cost Recoveries</td>
<td>€0</td>
<td>€309</td>
<td>€629</td>
<td>€964</td>
<td>€1,252</td>
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<tr>
<td>12</td>
<td>Investment returns</td>
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<td>€0</td>
<td>€0</td>
<td>€0</td>
<td>€96</td>
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<tr>
<td></td>
<td>Licensing and Investments</td>
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<td>€309</td>
<td>€679</td>
<td>€1,070</td>
<td>€1,551</td>
<td>€3,610</td>
<td>2.5%</td>
</tr>
<tr>
<td></td>
<td>Total REVENUES</td>
<td>€23,911</td>
<td>€26,630</td>
<td>€29,120</td>
<td>€31,461</td>
<td>€32,642</td>
<td>€143,764</td>
<td>100%</td>
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<td>Management &amp; Admin</td>
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<tr>
<td>14</td>
<td>Pre-incorporation Expenses</td>
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</tr>
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<td>15</td>
<td>Oncode Base Research Support</td>
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<td>16</td>
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<tr>
<td>17</td>
<td>Research Support</td>
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<tr>
<td>18</td>
<td>Valorization Operations</td>
<td></td>
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<tr>
<td>19</td>
<td>Valorization Funds</td>
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<tr>
<td></td>
<td>Total Expenses</td>
<td>€23,680</td>
<td>€26,583</td>
<td>€29,084</td>
<td>€31,480</td>
<td>€32,599</td>
<td>€143,395</td>
<td>100%</td>
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<tr>
<td></td>
<td>Annual Surplus/Deficit</td>
<td>€231</td>
<td>€47</td>
<td>€36</td>
<td>€12</td>
<td>€43</td>
<td>€369</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
Notes to the Financial Projections

(All amounts € x 1,000)

1. KWF Kankerbestrijding

Under the terms of the KWF Kankerbestrijding – Oncode Contribution Agreement, KWF will provide Oncode with €63,698 (€12,740 per year) during Phase I: 2017-2022. Subject to a positive mid-term review in 2021, KWF Kanderbestrijding intends to renew its funding commitment for Phase II: 2022-2027. Funds loaned by KWF Kankerbestrijding to Onco Research to facilitate pre-incorporation costs of Oncode are credited against KWF Kankerbestrijding’s 2017 financial obligations to Oncode and show in the projection as Pre-Incorporation Cost (note 14). The annual KWF Kankerbestrijding funding is comprised of €8,240 from its base budget and €4,500 to be raised by KWF through an Oncode dedicated fund raising campaign.

2. Ministry of Economic Affairs – Future Fund

The Future Fund is a program of the Ministry of Economic Affairs that includes an allocation of €20,000 targeted in support of thematic technology transfer. Under the Future Fund – Oncode Funding Agreement (the terms of which are under negotiated), Oncode will receive €12,500 over a seven year period (Phase I: €10,550; Phase II: €1,950). The annual allocation from the Future Funds will be directed to the Oncode valorization funds: patent fund (note 20); technology development fund (note 21); and Oncode Oncology Investment Fund (note 22). Under the general terms of the Future Fund program, funding is provided through a loan. The loan matures in fifteen years and requires a minimum 50% payback. This payback will be financed through: Oncode’s 10% share of net licensing revenue (note 10); IP cost recoveries (note 11); and the equity holdings (including liquidations) resulting from investments from the Oncode Oncology Investment Fund (note 12).

3. Top Sector Life Sciences & Health

The Topconsortia for Knowledge and Innovation (TKIs) is a program in which every €1 invested by the private sector in research and development at a research organization generates a €0.25 allowance that will be invested in new public-private research. The TKI Life Sciences and Health (“TKI-LSH”) funding is provided to Oncode through a program agreement with Topsector Life Sciences & Health. KWF has allocated its entire 2015, 2016 and 2017 TKI allowance to Oncode (€15,625). In addition, funds flowing to Oncode from industry sponsored R&D (€1,000 (2017) increasing to €4,000 (2021) – note 8) and a TS LSH supplement (€240 per year) will generate a total TKI allowance of €17,325 during Phase I. Under the general terms of TKI-LSH, the TKI allowance must be spent within five years from the date of allocation on eligible research expenditures (research staff salaries and bench fees) on research conducted in collaboration with industry. For the purposes of this program, the TKI funds will be allocated to the Onco Base Research Support (note 15) and the forecasted industry sponsored research (note 8) will
fulfill the requirement for minimum cash and in-kind industry contribution to total project costs.

4. Ministry of Education, Culture and Science

The Ministry of Education, Culture and Science (OCW) has committed €2,239 a year for Phase I: 2017-2022. The funding from this Ministry will be combined with the funding from the Ministry of Health, Welfare and Sport (note 5) and flow through ZonMw to Oncode. In order to comply with State Aid regulations, these funds will be targeted at Onco Base Research Support (note 15).

5. Ministry of Health, Welfare and Sport

The Ministry of Health, Welfare and Sport (VWS) has committed €2,239 a year for Phase I: 2017-2022. €2,000 per year will be combined with the funding from the Ministry of Education, Culture and Science (note 4) and flow through ZonMw to Oncode. In order to comply with State Aid regulations, these funds will be targeted at Oncode Base Research Support (note 15). The remaining €239 per year will flow through dedicated funds reserved for Oncode in the ZonMw Translational Research Program (note 6).

6. ZonMw Translational Research Program

At the request of VWS, ZonMw has reserved €1,198 under their Translational Research Program for Oncode. These funds will be used to support the Clinical Proof-of-Concept program.

7. Partner Institutions

The partner institutions are those research institutions that employ the Oncode PIs and their research groups. Currently, the partner institutions include: NKI, Hubrecht Institute, UMC Utrecht, Erasmus MC, LUMC, AMC, Radboudumc, Radboud University and Princess Máxima Center. The partner institutions will collectively contribute €958 to Oncode. Each partner institution’s contribution will be proportional to the number of Oncode PIs in their institution divided by the total number of Oncode PIs.

In addition to the cash contribution, each institution is committing the participation of the entire PI’s research team (PhD students, postdoctoral fellow, research technicians), 550 researchers in total and their related research costs (bench fees, equipment, overheads). This in-kind contribution is estimated at €60 million per year.

8. External R&D Funding

Oncode will be responsible for all research relationships with industry. In addition, Oncode may take a lead or coordinating role in some international research funding programs including grants from the European Union, NIH and foundations.
9. Fee-for-Service

Oncode will make its valorization services available for non-Oncode PIs and other oncology research institutes on a fee-for-service basis. These services may include business development, intellectual property management and project management. Exploratory discussions have been held with Hubrecht Organoid Technology (HUB) and Princess Máxima Center. In addition, at the request of a partner institution or KWF Kankerbestrijding, Oncode will provide fee-for-service support on an individual project basis.

10. Licensing Revenues

Oncode will derive revenues from the licensing of intellectual property under its management. Revenues may include a combination of royalties, up-front fees, milestone payments and proceeds from equity liquidation. For each license, gross income is first applied to the recovery of out-of-pocket costs (patent fees). Oncode will retain 10% of gross income in compensation for creating the licensed intellectual property in proportion to inventorship. While each institution has its own internal distribution formula, on average inventors receive 25% of net revenues with the remaining 75% distributed among the research group, central administration, technology transfer office and the academic department. Oncode will seek the commitment from each institution to ensure that within their distribution formula, a majority of the 70% revenues is directed to support oncology research.

11. IP Cost Recoveries

Under the terms of a license agreement, Oncode will normally retain responsibility for ongoing intellectual property management. Provisions will be made for both the recovery of past patent costs (when possible) and ongoing patent costs (required). Income from IP cost recoveries will be used to repay the loan under the Future Fund program (note 2).

12. Investment Returns

As part of its normal operations, Oncode will obtain securities (convertible loans, equity, options) in spin-off and affiliated companies as consideration for licensing intellectual property and/or capital investment. Oncode will retain sole authority to manage these equity investments. Proceeds from the sale of equity related to licensing transactions will be treated as licensing revenue and distributed according to the above formula. Proceeds from investments of the Oncode Oncology Investment Fund are solely for the account of Oncode and will be used to repay the Future Fund loan (note 2) with any excess amounts re-invested in the fund.

13. Management and Administration

Management and administration (M&A) expenses concern the staffing, operations and project costs related to the management and operations of Oncode. This includes support costs for the Supervisory Board and International Advisory Board. Staff will provide support in general
management, finance, human resources, communications, information technology and facilities. M&A expenses represent 5.2% of Oncode’s total expenses.

14. Pre-Incorporation Costs

On 12 April 2016, the Foundation to Incorporate an Oncological Research Institute (“Onco Research”) was incorporated as a not-for-profit organization with the purpose of performing all of the tasks required to launch Oncode. This included the development and international review of the Oncode strategic plan; negotiating funding agreements with all of the funding partners; negotiating affiliation agreements with each of the partner research institutions and developing the operational plans for Oncode. KWF Kankerbestrijding entered into a loan agreement with Onco Research which provided for up to €1,520 to Onco Research to finance its operations. The €1,520 loan is an advance on KWF’s €12,740 commitment to fund Oncode’s first year of operations (note 1).

15. Oncode Base Research Support

The Onco base research support provides annual grants (senior PIs - €250, junior PIs - €150) to each of Oncode’s PIs. At inception, this will provide approximately €10,000 in support to Oncode’s 43 founding scientists. Annually, an additional €3,000 is reserved to recruit and support additional PIs, including €1,200 reserved for the Female Investigator Program. Partner Institutions are permitted to charge a maximum of 10% of these funds in support of the indirect costs of research. This base level of research support enables the PIs to engage in projects under the six research themes.

16. Oncode Targeted Programs

Oncode has targeted funds to promote collaboration and enhance the research capacity and effectiveness of researchers across Oncode. These targeted programs include:

- Equipment and Infrastructure: €2,000
- Clinical Proof-of-concept: €2,500
- Technology Access: €500
- Institutional Initiatives: €1,000

17. Externally Funded Research

All of Oncode’s research will be undertaken at the partner institutions by the PIs and their research teams. Accordingly, the majority of the external research funding (note 8) will be transferred to partner institutions to cover the direct and indirect costs of research. To the extent that Oncode provides direct project and financial management services, it will retain a portion of the external research funding to cover its direct costs.
18. Valorization Operations

Valorization expenses relate to the staffing and operation of the Oncode valorization team. Staff will provide support in business development, IP management, contract administration, clinical and entrepreneurial mentoring and investment management. Staffing is forecast to grow from eight (2017 start-up) to fourteen (2022 full operations) and includes additional staffing required for fee-for-services operations (note 9). Direct project costs will be paid from dedicated funds for IP protection (note 20), technology development (note 21) and seed investment (note 22). Valorization expenses, including project fees, represent 15.1% of Oncode’s total expenses.

19. Net Licensing Revenue Distribution

Oncode will derive revenues from the licensing of intellectual property under its management (note 9). The net licensing revenue (gross licensing revenue less legal costs and 10% Oncode fee) is divided between the partner institutions responsible for creating the licensed intellectual property in proportion to intellectual contribution.

20. IP Protection

IP protection includes the out-of-pocket costs for preparing, filing, prosecuting and maintaining Oncode’s IP portfolio. Costs are predominantly related to patenting, but may also include fees related to copyright, data base and trademark registration. Forecasted expenses include provision for Oncode generated IP, including legacy filings transferred from Partner Institutions (€2,000), and IP from fee-for-service engagements (€500).

21. Technology Development

Expenses related to projects designed to: reduce technical uncertainty such as proof-of-concept, prototype development and scale-up; produce data to confirm and expand patent claims; and conduct third party market research. Individual projects will range in value from €10 to €150. Where possible, external funds will be used to cost-share and augment project funding.

22. Oncode Oncology Investment Fund

Oncode will provide investment funding for both spin-off (IP-based) and affiliated (people-based) companies. Investments may be made in the form of convertible debentures, common or preferred shares, options and warrants. Total investment in a single entity may not exceed €1,000, with a typical investment profile of: pre-seed – €50; seed – €200; A-round – €500, B-round – €250. All investments beyond the pre-seed stage will be syndicated with third party investors. During Phase I, Oncode forecasts the creation of four spin-offs and eleven affiliated companies. Oncode forecasts investing €3,410 in these companies during Phase I. An additional €1,950 will be available from the Future Fund to support follow-on financing in years 6 and 7.
Assessment and Monitoring Processes

Committed to learning, adapting to change

Oncode learns from its successes and setbacks. Oncode keeps adapting to a rapidly changing field – and ensures it grows in the most encouraging direction.

Research teams, as well as the Institute, are evaluated not only on scientific excellence but on collaboration performance and practical applications as well. If we want to be outsmarting cancer, impacting lives, we need to ensure that we are tracking on our strategic objectives along the journey. That means that we must set ambitious yet realistic goals, monitor our performance on a continuous basis to inform management decisions and establish clear criteria for our regular performance review. Research teams that contribute successfully to our mission will be invited to continue with Oncode for the following term.

The three principal categories for monitoring and assessing Oncode’s progress are:

1. Scientific excellence;
2. Collaboration; and
3. Valorization.

The assessment and monitoring processes are tailored to the needs of each phase of Oncode’s operations.

<table>
<thead>
<tr>
<th>Phase 0: Start-up</th>
<th>Phase 1A</th>
<th>Phase 1B: Mid-term</th>
<th>Phase 2</th>
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</thead>
<tbody>
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<td>Year 2</td>
<td>Year 3</td>
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<td>• Performance</td>
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<td>• Targets</td>
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<td>• Outlook</td>
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<td></td>
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<td>upcoming year(s)</td>
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- Assessment: IAB
- Approval: Supervisory Board
- Regular monitoring:
  - Oncode Research Management Committee
  - Oncode Management Board
  - Annual advising:
    - IAB

- Assessment: IRC
- Renewal funding:
  - Funders
  - Renewal funding PIs:
    - Oncode Management
Phase IA (2017-2021): Initial four years of operations

The primary intent of the monitoring and assessment process during phase IA is to monitor performance and guide internal resource allocation.

The Managing Board, with the assistance of the Research Management Committee, will monitor the progress of Oncode. In the first year of operations, Oncode will put systems in place that support reporting from the PIs and for the valorization team. The Managing Board will report on Oncode’s progress on the strategy execution at each Supervisory Board meeting.

Annually, the International Advisory Board will provide a qualitative review of Oncode’s performance and comprehensive advice on all aspects of Oncode’s performance at the institutional level as well as on the level of the scientific themes. Based on the annual reports from the PIs and the valorization team, Oncode will provide the International Advisory Board with an annual report covering the overall performance of the preceding year and an outlook for the upcoming year(s). This report will include progress against strategic objectives by providing impact statements, performance indicators and financial reports. During the site-visit the International Advisory Board will meet with the Managing Board, the Research Management Committee and a selection of the PIs.

The Managing Board will report annually to Oncode’s funding partners, including the partner institutions. This report will include data on the performance of Oncode described in the impact statements and indicated by the deliverables on the institutional performance indicators, an outlook for the upcoming year(s) and the report of the International Advisory Board accompanied by Oncode’s response. The exact reporting requirements will be determined in the start-up phase and will be appended to both the contribution agreements and the affiliation agreements with the partner institutions.

The review and assessment criteria of the Oncode programs (technology access, equipment and infrastructure, clinical proof-of-concept and female investigators program) will be established with the development of those programs.

Phase IB (2020/2021): Renewal

The intent of the mid-term assessment process in Phase IB is to confirm Oncode’s Phase I performance and assess its Phase II (2022-2026) strategic plan, resulting in renewed funding. An independent International Review Committee 2020/2021 will perform the review in 2020.

On institutional level, Oncode’s performance will be assessed against its progress in achieving its strategic objectives, described in the impact statements and indicated by the deliverables on the institutional performance indicators and the strength of its Phase II Strategic Plan.

Individual PIs will be assessed on their past performance in Oncode and their potential contribution to the Oncode’s Phase II strategy. Each PI will report on the PI impact indicators and future plans for Phase II. Based on these reports, the contribution of the PI to Oncode will be peer reviewed by a PI Evaluation Committee. The peer review process will be further developed...
during the start-up phase of Oncode. Research teams that have not met expectations will no longer participate in Oncode, and their resources will be reallocated to well-performing teams and to selecting new PIs and teams.

**Phase II (2022/2026): Second phase of operations**

The Phase II strategic plan will cover the monitoring and assessment processes, including but not limited to a transparent process description of:

- the assessment of the junior PIs for promotion purposes; and
- the selection of new PIs and teams.

**Impact statements on institutional level**

An impact statement provides qualitative insight in the progress of Oncode towards its strategic objectives. The impact statement on each of the three principal categories, scientific excellence, collaboration and valorization, covers:

- **an overview of the activities of Oncode on achieving the objectives, including process steps;**
- **(intermediate) results that have been achieved (outputs and outcomes); and**
- **an update on the strategy to achieve the objectives.**

Each objective requires a different format for reporting on its progress. Indicators from the broader set of Science in Transition indicators, developed by UMC Utrecht, will be incorporated where applicable.

The impact statements allow in-depth discussion on the progress of Oncode. For monitoring purposes, the impact statements will be accompanied with expert advice from the International Advisory Board. In the mid-term assessment the impact statements will be peer-reviewed by the International Review Committee.
Performance indicators on institutional level

The performance indicators and their corresponding deliverables indicate the progress of Oncode towards its strategic objectives. The deliverables should be peer-reviewed in combination with the qualitative impact statements. Performance indicators have been defined within Oncode’s three principal categories. The reporting format on these indicators will be developed during the start-up phase of Oncode. This will be assessed by the International Advisory Board and must be approved by the Supervisory Board.

Scientific excellence

1. Top tier publications;
2. The mean normalized citation score;
3. International standing PIs; and
4. Competitive funding acquired on scientific grants.

Collaboration

1. Internal Oncode: the number of joint publications + joint grant proposals + joint PhD supervisions;
2. External Oncode: the number of joint publications + joint grant proposals + joint PhD supervisions;
3. Sharing of materials, resources and techniques; and
4. Quality of Oncode’s knowledge community, which includes among others participation in discussions, exchange of ideas, courses, comments and communication with and involvement of stakeholders.

Valorization

1. Discoveries advanced to the clinic;
2. Number and quality of patent filings;
3. Number of companies working together with Oncode and the nature of the collaboration (number of industry contracts, technology licensing, company creation and amount in Euros of industry funding); and
4. Pilots on affordable health care.

A baseline of the performance indicators will be created during the start-up phase of Oncode. This baseline, along with the international standards for scientific and valorization excellence will be used to establish the Phase I targets for Oncode. These targets, and any subsequent adjustments, will be assessed by the International Advisory Board and must be approved by the Supervisory Board and the funding partners.
Impact indicators on PI level

The PI impact indicators provide quantitative and qualitative insight in the contribution of the PIs to the strategic objectives. The deliverables of a PI on these indicators will be peer reviewed. The peer review process will be developed during Oncode’s start-up phase.

Based on the broader set of Science in Transition indicators, we have defined an initial set of PI impact indicators. The final set of indicators will be determined during the start-up phase, together with a workable format for reporting. The International Advisory Board will assess the final indicators and the Supervisory Board needs to approve.

Scientific excellence

1. Description of the questions that are being pursued and how the answers will contribute to Oncode’s mission;
2. Demonstrate how the main research question fits the existing knowledge;
3. Top tier publications;
4. Invitations for international scientific meetings;
5. Competitive funding acquired on scientific grants;
6. Three most important research products for peers, consisting of key publications and other forms of research output;
7. Three most important examples of recognition from peers, e.g. science awards/scholarly prizes/personal grants;
8. Involvement of patients and other stakeholders? How were they involved in formulating research questions;
9. Availability of data management plans;
10. Rigor toward high standards of reproducibility and record keeping;
11. Publication of raw data; or the availability of data for external use; and
12. Open access publications.

Collaboration

1. Three most important examples on how research products are being used by peers;
2. Joint publications (specifically indicate when collaborating with clinicians);
3. Joint grant proposals (specifically indicate when collaborating with clinicians);
4. (Joint) PhD supervisions; and
5. Collaboration on research infrastructure and facilities.
6. Contribution to the Oncode’s knowledge community, which includes, among others, participation in discussions, exchange of ideas, courses, comments and communication with and involvement of stakeholders

**Valorization**

1. Three most important examples of research products for societal target groups (for example policy-makers and non-academic readers);
2. Possible users of research findings are demonstrably involved in the project, e.g. other (clinical) research groups, general practitioners, nurses, small and medium enterprises, pharmaceutical and medtech companies;
3. Membership of (guideline) committees, policy panels; lectures for policy makers and other stakeholders; publications in “grey literature”; coverage in general media; and
4. Collaboration with the valorization team.
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>AMC</td>
<td>Amsterdam Medical Center</td>
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<tr>
<td>BBMRI-NL</td>
<td>European Biobanking and Biomolecular Resources Research Infrastructure</td>
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<tr>
<td>CPCT</td>
<td>Centre for Personalized Cancer Treatment</td>
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<td>Erasmus MC</td>
<td>Erasmus University Medical Centre</td>
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<tr>
<td>Hubrecht Institute</td>
<td>Hubrecht Institute for Development Biology and Stem Cell Research</td>
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<td>KWF</td>
<td>KWF Kankerbestrijding (Dutch Cancer Society)</td>
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<td>KNAW</td>
<td>Royal Netherlands Academy of Arts and Sciences</td>
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<tr>
<td>LUMC</td>
<td>Leids Universitair Medisch Centrum (Leiden University Medical Center)</td>
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<tr>
<td>EZ</td>
<td>Ministry of Economic Affairs</td>
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<td>OCW</td>
<td>Ministry of Education, Culture and Science</td>
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<tr>
<td>VWS</td>
<td>Ministry of Health, Welfare and Sport</td>
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<tr>
<td>NKI</td>
<td>Netherlands Cancer Institute</td>
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<td>NWO</td>
<td>Netherlands Organization for Scientific Research</td>
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<tr>
<td>PCOCs</td>
<td>Primary cancer organoid cultures</td>
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<td>PDX</td>
<td>Patient derived xenografts in mice</td>
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<tr>
<td>PMC</td>
<td>Princess Máxima Center for pediatric oncology</td>
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<tr>
<td>Radboudumc</td>
<td>Radboud University Medical Centre</td>
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<td>REGMED XB</td>
<td>REGenerative MEDicine crossing Borders</td>
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<td>Utrecht University Medical Center</td>
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<tr>
<td>ZonMw</td>
<td>Netherlands Organization for Health Research and Development</td>
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Oncode Institute

Outsmarting cancer
Impacting lives

Manifesto & Values
The Oncode Manifesto

Outsmarting cancer, impacting lives

The collection of diseases we call cancer afflicts an alarming number of people, making it a leading cause of death worldwide. There’s a tremendous need to develop new knowledge and methods to outsmart these diseases. Oncode is an independent institute dedicated to understanding cancer and translating research into practice more efficiently. Oncode, starting from a deeper understanding of the basics of cancer, works to come up with better treatments and improved diagnostics. This will take time. Only a coordinated and sustained effort will bring us closer to our goal: helping more patients survive, improving the quality of life for those afflicted, and ultimately curing cancer.

United against a divisive enemy

Effective cancer research is unthinkable without collaboration. The field is immense and new developments are occurring all the time, so partnerships are key – whether internal, external or interdisciplinary. That’s why Oncode brings together top researchers and joins forces with leading public and private partners. Its aim? To foster a culture of sharing knowledge among teams that are embedded at partner institutions, thus strengthening cancer research communities in the Netherlands and around the world.

High standards, greater impact

Oncode presents a new model for excellence in science, inspired by international best practices and founded on the insights of leading oncology experts and the needs of society. In every aspect of its operation – from fundamental research to developing technologies to the teams of professionals it attracts – the institute actively aims high. Oncode provides exceptional resources, helping accomplished scientists and top talents come together under the best possible conditions.

Building a knowledge network, not a building

Oncode builds on the vast body of existing cancer research. Selected research teams will continue to work at partner institutions. No new building will be constructed, because Oncode operates as a virtual institute, creating a digital platform for collaboration and debate. This innovative approach, in addition to saving time, keeps the institute’s environmental footprint as light as possible.
Molecular research as the foundation

Providing each patient with the best possible care requires a fundamental understanding of cancer. True innovation in treatments relies on new insight into the basic mechanisms of cancer development. That’s why the institute focuses on molecular oncology. Oncode is aware it will take many small steps before a significant leap can be made. A personalized approach is the most promising for eliciting scientific breakthroughs.

Translating research into clinical practice

If fundamental research is one side of the coin, clinical research is the other. Oncode connects its research activities with the best clinical capabilities available, thereby maximizing the relevance of research questions. This accelerates the development of applications that benefit patients. Oncode provides the funding and the tools to transfer technologies, enabling them to reach the marketplace effectively and affordably. A specialized team focused on transforming research results into real-world advances works to build an enterprise, establishing value and creating manifold partnerships.

Stories open up science

The institute shares new insight and developments with donors and funders, the scientific community and the public at large. Learning from patient stories and openly sharing its progress and findings through the scientific world and beyond, Oncode aims to promote science in a new way – one that is transparent and inspirational.

Today’s wisdom fosters future talent

Oncode aims to inspire a constant flow of knowledge to a new generation of scientists. The institute grows by having a healthy influx of talented young researchers. The aim is to be diverse, welcoming talent of all backgrounds. Programs are in place, offering career support and leadership courses to promising new faces. Together advancing the field of oncology in the Netherlands and abroad.

Committed to learning, adapting to change

Oncode learns from its successes and setbacks. Research teams are evaluated not only on scientific excellence but on practical applications and collaboration performance as well. Programs that do not deliver in this regard will make way for the most effective projects. Oncode keeps adapting to a rapidly changing field – and ensures it grows in the most encouraging direction.
Our Values

Onco has established the following values to guide us in all we do: from inspiration to action.

- **excellence** the quality of being outstanding or extraordinary
- **collaboration** the dedication to working with others toward a shared goal
- **creativity** the use of imagination and original ideas to create something new
- **flexibility** the willingness to change course or reach a compromise
- **engaged** the drive to build relationships with those who benefit from our work

These values only have meaning internally when we share them as an inspirational call to action.

- **Be excellent:** From people to publications, from research to writing, from concepts to communications, excellence is the standard we apply to everything we do. Only by aiming high can we push ourselves and each other to new levels of achievement.

- **Be united:** Working together to the same end, we at Onco embrace collaboration. Open to the insights and criticism of colleagues and others. We don’t hide away our knowledge, but share it as a team. Only together can we move forward faster.

- **Be creative:** We value non-conformist ideas, and welcome challenges to the accepted. At Onco, our creativity is not limited to the lab; we all use our imaginations to find smart, modern solutions.

- **Be flexible:** We are eager to learn, willing to grow and ready to adapt. Embracing change as a constant characteristic of our field and of our work. Without compromising on quality.

- **Be engaged:** Our research is informed by needs and realities of patients, clinicians and industry. The end-result is affordable and open for others to build on. As people rely on our findings and their life-changing potential, this is the only route to success.